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CONTENTS

SOME ASPECTS OF TESTICULAR PHYSIOLOGY

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Concepts regarding testicular physiology have changed considerably during recent years and are still in a condition of flux. Considerable knowledge has been gained concerning the testis hormone which causes comb growth when injected into capons. Much of this advance has been the result of investigations by Koch[1] and his associates. This comb-growth-producing substance has been isolated by David, Dingemanse, Freud and Lacqueur[2] and is called testosterone.

A substance, probably a metabolic derivative of testosterone with very similar but less active physiological properties, is found in urine. This has been isolated by Butenandt[3] who has called it androsterone. Urinary extracts containing androsterone have been used in experimental work in this laboratory, and the name "androtin" has been used to designate these extracts. The purpose of this paper is to summarize the evidence which leads us to believe that prostatic hypertrophy may be the result of endocrine imbalance, and that a second testicular hormone exists and is involved in the production of this condition.

Moore[4] has recently discussed the physiology of testosterone thoroughly, and it will therefore be reviewed rather briefly in this paper. Its chief function appears to be the stimulation of growth and maintenance of the whole male fecundatory mechanism. Recently, it has been demonstrated by Walsh, Cuyler and McCullagh[5] that this is true not only for the secondary sex glands but for the testes themselves. Following hypophysectomy, complete atrophy of the primary and secondary sex glands always occurs. This atrophy commences three or four days following hypophysectomy, and the changes are almost complete in twenty days. It was found that the daily injection of nine bird units of androtin into hypophysectomized rats over a period of twenty days maintained the testes, seminal vesicles, and the prostate glands of these experimental animals in a condition which could not be distinguished from the normal. The tubules of the testes and the epididymides of the hypophysectomized animals treated with androtin contained more spermatozoa than did the normal controls.

The androtin used in these experiments was made by the continuous extraction of urine with carbon tetrachloride. The carbon tetrachloride was removed by distillation and the extracts purified by distribution between fat solvents. The extract was eventually dissolved in sesame oil and heated in the autoclave at 120 degrees Centigrade for one-half hour. We thus feel that it was not contaminated with pituitary-like

hormone which is occasionally found in the urine of men, and which acts as a gametogenic substance.

Testis hormone has many functions other than the maintenance of the sex mechanism. The most noticeable is that of the maintenance of the secondary sex characteristics. The growth and distribution of body hair is influenced by testicular function. In birds, the plumage and comb and wattles show normal male characteristics only when the testis hormone is present. The distribution of body fat in man and in animals is altered by castration. Due to the fact that epiphyseal closure is delayed, skeletal proportions are abnormal in the absence of testis function—the long bones being relatively longer in a eunuch than in a normal man.

Clinicians have known for many years that there is a close relationship between the adrenals and the sex glands. Hirsutism, virilism and pubertas praecox have frequently been known to be associated with adrenal tumors. Following castration in animals, there is a definite hypertrophy of the adrenals. That this hypertrophy is due to absence of the testis hormone is shown by the fact that it can be controlled by the injection of androtin.[6]

There is ample evidence to prove that testis hormone exerts a profound influence over the pituitary gland. Following castration, a marked change in the histologic appearance of the pituitary glands occurs. The percentage of basophil cells rapidly increases, and some of these basophil cells become vacuolated and finally form signet ring cells—the so-called castration cells of the pituitary gland. Reese and McQueen-Williams[7] claim to have demonstrated that in the castrated rat, basophil cell formation can be prevented or considerably modified by the administration of 4.4 bird units of testicular extract. Nelson[8] failed to control the pituitary glands of castrated male rats with 7.5 bird units of testicular extract daily, although the same dose prevented formation of basophil cells in gonadectomized females.

We have performed another series of experiments which demonstrate that androtin has a marked influence over the pituitary gland.[9] When two rats are united surgically in parabiotic union so that their peritoneal cavities are continuous, diffusible water-soluble substances will pass from one animal to the other. The gonadotropic hormone of the anterior lobe of the pituitary gland is a substance of this type. If one of a pair of parabiotic animals is castrated, its pituitary gland becomes hyperactive as evidenced by the fact that its parabiotic partner shows every sign of pituitary stimulation. If this normal partner is a male, the excessive amount of pituitary hormone coming from the castrated partner stimulates the testes of the normal partner to the production of large quantities of testosterone with the result that its prostate and

seminal vesicles become hypertrophic. We found that if sufficient androtin is injected into the castrated partner to prevent its prostate from becoming atrophic, none of the signs of pituitary hyperactivity are observed in the normal animal.

With some of these and with other facts in view, Moore[10] postulated a theory of pituitary-gonadal interrelationship. According to this theory, the gonadal-pituitary mechanism is self-regulatory. If the testes produce insufficient quantities of testosterone, the pituitary gland is not held in proper control, and it produces larger amounts of gonadotropic hormone. In that manner, the pituitary gland stimulates the testes to the production of the proper amount of testosterone. Conversely, if excessive amounts of testosterone are produced, pituitary depression results and in turn, testicular function is retarded. Moore[11] has also discussed the possibility that two hormones may be elaborated in the testes. If this proves to be the case, his theory of pituitary-gonadal interrelationship will have to be extended to include the second endocrine product of the testes.

Our investigations concerning androtin commenced in 1930 when a considerable quantity of this substance was made from urine in order to treat patients who suffered from hypogonadism. The androtin thus prepared for this study was assayed by injection into capons and also by injection into castrated rats. Each rat was sacrificed and carefully examined at the completion of the test, and it soon became apparent that a castrated rat could not be maintained in a completely normal condition by the use of this hormone.[6] Following castration, the secondary sex glands normally undergo complete atrophy, and the adrenals and the pituitary gland become hypertrophied. The administration of androtin will prevent atrophy of the secondary sex glands in castrated animals and will prevent hypertrophy of the adrenals but will not prevent the pituitary gland from becoming enlarged. Following our publication, Korenchevsky[12] made the same observation regarding the effects of androtin and more recently has repeated these observations using a synthetic comb-growth-producing material. From this, we deduced that there might possibly be a second testicular hormone, one property of which is to control the activity of the pituitary gland. For this hormone, the name "inhibin" has been proposed.[13]

Following this observation that androtin did not control the pituitary hypertrophy which followed castration, we investigated the literature to see whether other workers had discovered anything which might throw further light on the problem of the duality of endocrine function of the testes. A considerable quantity of information on the subject was already available, and other authors who had worked from entirely

different angles had reached the conclusion that the testes produced two hormones.

In 1923, Mottram and Cramer[14] studied the effect of irradiation on the rat and made a very significant observation. They noticed that following irradiation of the testes with roentgen rays, the tubular elements rapidly underwent degeneration and the interstitial elements remained normal. Accompanying these changes in the testes, there was a definite change in the pituitary gland which simulated that which follows castration. They found at the same time, that no atrophy of the secondary sex glands occurred. They concluded that one testicular mechanism controls the pituitary gland while another is responsible for the maintenance of the secondary sex glands.

Johnston,[15] working in collaboration with Dr. Lower, noticed that following irradiation of rats' testes and destruction of the tubular elements, prostatic hypertrophy resulted in some instances. This could be interpreted as being the result of destruction by the x-ray of the inhibin-producing mechanism of the testes, and prostatic hypertrophy would result from pituitary stimulation.

In 1926, Nukariya[16] studied the influence of saline extracts of testes on the pituitary glands of castrated animals and noted that these extracts altered the metabolic processes of the castrated animals but did not alter the number of basophil cells in the pituitary gland following castration. Only a very small amount of testosterone is found in the testes and from a quantitative point of view, one would not expect any effect from the administration of this hormone in a saline extract, particularly when one considers that it is not soluble in saline. This would indicate that there is a water-soluble hormone in the testes which influences pituitary activity. Lehmann[17] states that the injection of water-soluble testicular hormone into castrated rats will prevent the occurrence of histologic changes in the pituitary gland. Martins[18] has more recently studied the same problem and also claims that these aqueous extracts suppress the production of basophil cells in the pituitary glands of castrated rats. Witschi, Levine and Hill[19] experimented with rats which had received roentgen irradiation to the testes. They found that the tubules of the testes were destroyed while the interstitial elements were intact. The secondary sex glands were hypertrophied which showed that the testes were producing excessive quantities of testosterone. Using the parabiotic method, they demonstrated that these animals had hyperactive pituitary glands which, according to our interpretation, means that the inhibin producing properties of the testes had been destroyed, whereas the testosterone producing areas were intact as evidenced by the hypertrophied secondary sex glands.

Evans and Simpson[20] studied the effect of castration and cryptorchidism on the quantity of gonadotropic hormone in the pituitary gland. Following castration, the pituitary gland not only increases in size, but there is an increase in hormone content. The changes which take place in the testes in cryptorchidism are similar to those which follow roentgen irradiation. There is rapid degeneration of the tubular elements during the first month, whereas the interstitial cells persist for a considerable period. Following destruction of the tubular elements, but before the testes lose their power to elaborate testosterone, a definite change occurs in the pituitary gland. The change which occurs during cryptorchidism is similar to that which follows castration in that the pituitary glands of cryptorchid animals also contain a greater quantity of gonadotropic hormone than that in normal animals. In other words, the cryptorchid testis elaborates sufficient testosterone to maintain the secondary sex glands, but the mechanism which controls pituitary activity has failed.

Probably the most striking results obtained in the study of inhibin were those of Martins and his collaborators.[18] In their experiments with parabiotic rats, they attached a castrated animal to either a normal male or female. Following castration, the normal animal was influenced by the hyperactive pituitary gland of the castrated partner. These workers showed that when small quantities of testicular mush from either mature or immature animals were injected into the castrated animal, pituitary hyperactivity was prevented, and they pointed out that this suggested the presence of a second testicular hormone. McCullagh and Walsh[9] have confirmed the experiments of Martins and Rocha using adult male rats and in addition have demonstrated that the injection of aqueous extracts of testes into normal animals will decrease the pituitary activity and therefore produce prostatic atrophy. Myers[21] and his coworkers state that feeding desiccated testicular material to rats caused prostatic atrophy. We repeated his work and obtained apparently confirmatory results. More recently, however, we have had difficulty in duplicating these experiments.

Schrire and Zwarenstein[22] have studied the influence of the testes on creatinine metabolism in rabbits. They state that when aqueous extracts of testes are injected into castrated rabbits, the otherwise abnormally high daily output of urinary creatinine is diminished. Testicular preparations similar to those used by Professor Koch also have the same property; however, as stated above, one does not expect aqueous saline extract to contain more than insignificant traces of testosterone. It would seem to this author that these experiments indicate that inhibin may have some influence on creatinine metabolism. This problem is now being investigated here.

Recently reported experiments by Stein[23] on castrated immature rats indicate that the testes show signs of inhibin production long before there is any indication of a production of testosterone. If the animals are castrated when seven days of age, very marked pituitary hypertrophy occurs in two or three weeks. This is particularly interesting in that the castration of the adult rat frequently does not result in definite hypertrophy in less than two or three months. Hence, the pituitary of the immature animal is more sensitive to withdrawal of inhibin than is that of the adult animal.

There can be no doubt but that the experiments herein reported definitely indicate the production in the testes of the hormone inhibin. It has been our experience, however, that it is extremely difficult to obtain constant results using the techniques so far developed for the demonstration of this hormone. The problem is obviously in its infancy. Nearly all the work so far reported should be repeated and confirmed, and a method of assay must be developed before the work can progress in the proper quantitative fashion.

Clinical Considerations: McCullagh, McCullagh and Hicken[24] studied the effects of the administration of androtin to men suffering from hypogonadism. An insufficient amount of hormone was available to treat these patients for a long period of time; however, there seemed to be definite reasons to believe that the secondary sex glands in man could be stimulated by the use of androtin. In some instances after treatment, motile spermatoza were found in fluid obtained by prostatic massage in cases where none were found before. This is in accord with experimental findings in which androtin maintained the spermatogenic elements in hypophysectomized rats.

Other authors have not mentioned the great clinical significance of the hormone inhibin. The theory of dual endocrine activity of the testes offers an excellent explanation for prostatic hypertrophy in man. If the cells which produce inhibin fail before those which produce testosterone, one would expect hyperactivity of the pituitary gland to follow. The resultant excessive gonadotropic activity in the pituitary gland would cause stimulation of the cells of the testes which produce testosterone. It is known that testosterone is capable of producing prostatic enlargement in experimental animals, and there is no reason to believe that this may not also occur in man.

There are two facts which strongly support this theory of the etiology of benign prostatic hypertrophy. First, it has been known for years that castration in some cases will cure benign prostatic hypertrophy in man. This indicates that the condition is related to testicular activity. Moreover, several castrated patients who have been examined in this

institution have all been found to have atrophic prostate glands. Second, pituitary overactivity in benign prostatic hypertrophy has been demonstrated by Dr. E. P. McCullagh and Mr. Kenneth Cuyler in several patients suffering from prostatic hypertrophy. This has been so definite that a positive Friedman test of the same type as that which occurs during pregnancy has been observed.

The clinical application of this theory has been studied by Dr. William E. Lower who also has collaborated in the experimental work. Dr. Lower has reported his clinical findings in this issue of the Quarterly.

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TREATMENT OF BENIGN PROSTATIC HYPERTROPHY BY A NONOPERATIVE METHOD

WILLIAM E. LOWER, M.D.

At the June 1935 meeting of the American Medical Association at Atlantic City, I gave a clinical report on the treatment of benign prostatic hypertrophy by nonoperative methods before the Section on Urology.

In 1928, we began an experimental research to see if we could find a more tenable explanation of the etiology of benign prostatic hypertrophy. As a result of this experimental work, we believed that an endocrine imbalance was the most likely explanation, and D. Roy McCullagh has discussed our experimental findings in the paper presented in this issue.

In the first preliminary report at Atlantic City, we presented our results in the treatment of 40 cases of benign prostatic hypertrophy and since then, we have added 36 more, so that we now have 76 cases in which we have sufficient records to make the additional report. In spite of persistent efforts, a suitable method of assay has not been developed. For this reason, it has been impossible to determine what chemical fraction of the glands contains the hormone "inhibin," and equally impossible to know whether or not all our preparations were of the same strength and what dose of hormone each patient received. Each patient received the equivalent of 60 grams of fresh beef testicular material daily. The material was completely desiccated in vacuo at 60 degrees Centigrade and was administered in powder form in gelatin capsules.

The type of case in which we have used this medication has varied somewhat, but we have felt that it is most applicable in those cases in which the prostate is of moderate consistency and movable as determined by rectal palpation. Some of the patients had complete retention of urine, whereas others had varying amounts of residual urine and nocturnal frequency. The improvement of symptoms was generally manifested within a week or ten days after treatment was instituted, and maximum improvement was reached within from four to six weeks. No other type of treatment was used. In cases of complete retention, the patient was catheterized regularly or an indwelling catheter was used for a time until the patient could void. In the presence of residual urine or partial retention, catheterization was done only at stated intervals of from one to two weeks in order that any change in the amount of residual urine might be noted.

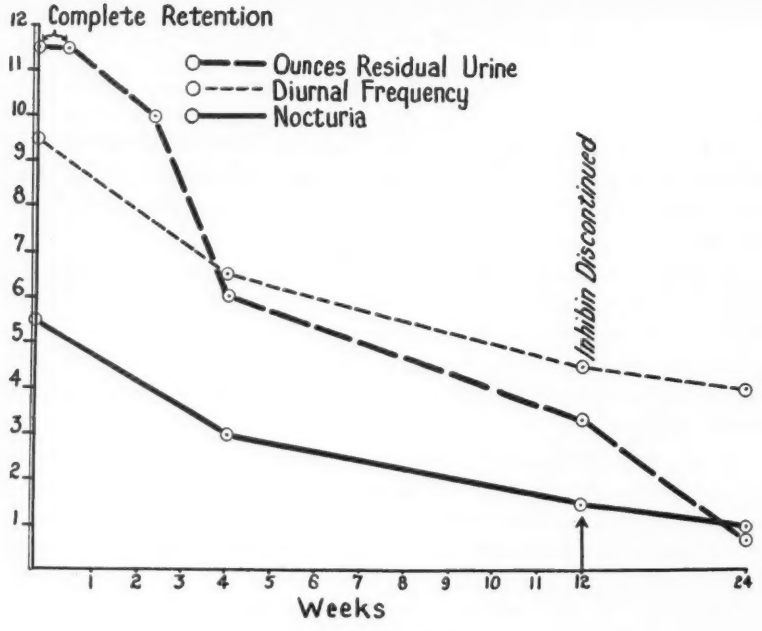

CHART I

The following cases are typical of those which respond to this treatment:

Case 1: The patient was a man, 66 years of age, who came to the Clinic complaining of complete urinary retention. Two or three years before this examination, difficulty in urination had begun which resulted in complete retention of five days' duration.

On cystoscopic examination, the bladder neck showed rather pronounced bilateral lobe intrusion and no median lobe was present. The prostatic urethra was markedly lengthened, and the lateral lobes met in the midline throughout this distance. Rectal examination revealed the prostate to be quite large but fairly firm.

Laboratory examination revealed the blood urea to be 48 mg. per one hundred cubic centimeters, and in view of the poor kidney function and nitrogen retention, it was decided to use medical treatment.

The patient entered the hospital and to care for the complete urinary retention, he was catheterized twice or three times daily. The capsules were administered, and for three weeks no improvement could be noticed. The patient then found that he was able to void a little between catheterizations and this improvement continued until five weeks after inhibin was started, when he was able to empty his bladder completely. He was discharged from the hospital and at that time, the blood urea had returned to a practically normal level, and he felt generally much stronger and better. Chart I shows this

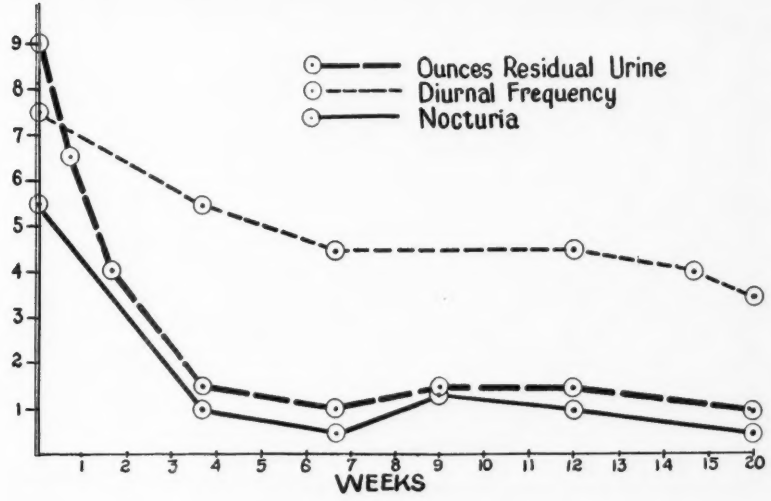

CHART II

patient's progress in regard to the ounces of residual urine, diurnal frequency and nocturia.

This patient now feels so well that he considers himself cured; he voids easily and has nocturia only once nightly.

Case 2: This patient was a man, 55 years of age, who came to the Clinic complaining of practically complete urinary retention. A very small amount of urine could be passed, and catheterization was necessary twice daily. These symptoms began seven years before our examination and several months before admission, nocturia had become a distressing symptom, occurring every 15 or 30 minutes.

Physical examination revealed no abnormalities except for the prostate which was markedly enlarged, smooth and of moderate consistency. Cystoscopic examination revealed an obstructive type of bladder and trilobar hypertrophy of the prostate gland with pronounced extravesical bilateral lobe enlargement.

This type of enlargement is that for which prostatectomy would be recommended but also the type in which one might expect satisfactory results after endocrine therapy. This latter method was accepted by the patient and treatment was begun. After ten days, the patient was able to void so well that catheterization was discontinued and three days later, only 55 cubic centimeters of residual urine were present when he was discharged from the hospital. Chart II shows the progress which this patient made.

This patient has been able to return to his work, is able to urinate almost normally and catheterization yields only a few cubic centimeters of residual urine. Nocturia occurs only once at most and occasionally it is entirely absent.

Case 3: The patient was a physician, 57 years of age, who came to the Clinic with complete urinary retention which had been present for two days

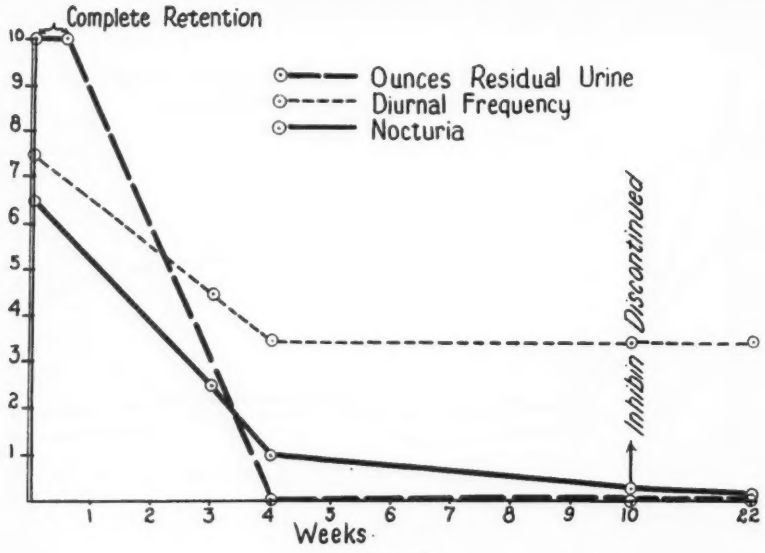

CHART III

and for which he had resorted to self-catheterization. Symptoms of obstruction had begun three or four years before our examination and nocturia from 8 to 12 times had been present for the previous six years.

Physical examination revealed trilobar hypertrophy of the prostate of a smooth, soft type; otherwise, the general physical condition was good.

The patient entered the hospital for treatment with inhibin which was administered three times daily. Intermittent and rather frequent catheterization was necessary during the first few days but after seven days, he was able to void so well that catheterization was discontinued and at the time of his discharge from the hospital—five days later, he was able to empty his bladder completely. (Chart III.)

When we last saw this patient, he considered himself absolutely well. He was able to void freely and easily with no hesitancy whatever. The voided urine was clear, and catheterization yielded no residual urine.

Chart IV shows another case in which the patient was admitted with complete urinary retention. Treatment with inhibin was begun, and nocturia and diurnal frequency were greatly lessened, and no residual urine was present after five weeks.

The first signs of improvement after treatment with inhibin was instituted were decreased nocturia, greater ease in voiding, increase in the size of the stream and reduction in frequency. All patients reported a feeling of general well being. In a few instances, an increase in symptoms was reported, and the medication was discontinued.

In this series of 76 cases in which inhibin has been used, 48 cases

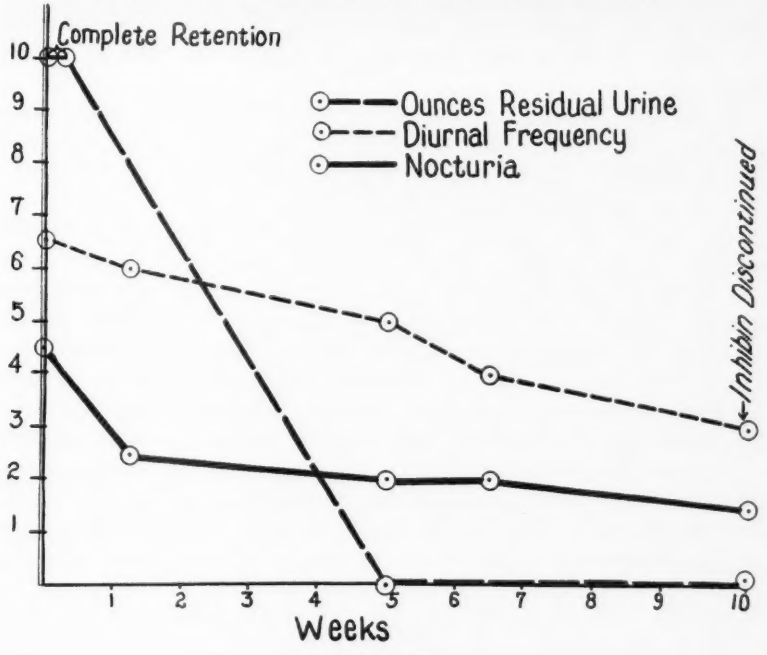

CHART IV

have been improved. The type of gland which was present is shown in the following table:

Type	*Improved and free from symptoms*	*Unimproved*	*Total*
Simple bilateral hypertrophy	14	10	24
Trilobar hypertrophy	17	9	26
Middle lobe hypertrophy	4	4	8
Not specified	13	5	18

The average age of the patients was 67.0 years, the youngest in the group was 54 and the oldest 77 years of age. The longest duration of symptoms in the improved cases was 2.01 years and in the unimproved cases 5.1 years.

It is obvious that a fibrous or a malignant growth would not be suitable for this type of treatment, nor would we expect any benefit to result in those cases which are complicated by such conditions as diverticula of the bladder. It has been stated that 20 per cent of the cases which are diagnosed clinically as benign prostatic hypertrophy prove at operation or autopsy to be malignant. This and the reasons just cited may well account for the failure of 28 of the 76 patients to react favorably to

the treatment. When more refined methods for isolating the hormone are found, we believe the percentage of improvemnt will be greatly increased.

In the unimproved cases, the known causes for the failure to obtain satisfactory results has been as follows in four cases: Previous punch operation and cystotomy, sclerotic type of middle lobe, very atonic and distended bladder and associated diabetes.

The exact *modus operandi* by which this benefit is obtained is not certain. In many cases, there has been no perceptible change in the size of the prostate by rectal examination and neither has there been a very discernible difference in appearance by histological section, although in experimental animals, marked change is noted both grossly and microscopically. Perhaps insufficient time has elapsed for these changes to be apparent. It may be that this group represents the percentage of cases that would improve under ordinary conditions without medication but if this be true, then we have been operating upon too many cases of this type of prostatic hypertrophy. We believe this change in the symptoms to be due to the medication, and we also appreciate, however, that a larger number of clinical cases are necessary before final conclusions can be reached.

Conclusions

Researches with experimental animals demonstrated that a certain type of benign prostatic hypertrophy is the result of an endocrine imbalance. It was then postulated that benign prostatic hypertrophy in man was probably due to a hormonal deficiency of testicular origin. Forty cases of benign prostatic hypertrophy have been treated with a preparation supposedly containing the hormone in question. Sixty-five per cent of the patients have shown definite improvement with regard to their symptoms and general health.

GRANULOPENIA (AGRANULOCYTOSIS)

RUSSELL L. HADEN, M.D.

In 1922, Schultz[1] described four patients with gangrenous throat lesions and marked leukopenia due to a decrease or absence of granular cells from the peripheral blood. The patients were all women of middle age, all died, and at autopsy very few myeloid cells were found in the bone marrow. Schultz designated the condition, agranulocytosis, and considered it a definite clinical entity. Since this first report, many similar cases have been reported, largely from Germany and America. Numerous names other than agranulocytosis, such as, agranulocytic angina, malignant neutropenia, idiopathic neutropenia, pernicious leukopenia, granulocytopenia, and granulopenia have been suggested to indicate the syndrome described by Schultz. The word, granulopenia, best describes the condition since it is primarily a decrease in the granular cells of the blood. Idiopathic granulopenia refers to granulopenia occurring without apparent cause. The subject has been in a confused state but increasing study suggests that leukopenia and necrotic lesions represent a symptom complex and not a clinical entity. It is now known that every degree of severity of both clinical symptoms and blood findings may be encountered. What Schultz observed was a high degree of bone marrow involvement which often occurs in much milder form as a result of the same etiologic agent or agents. It is now also evident that changes observed in the peripheral blood only reflect bone marrow disease, so no correct picture of the condition is possible without correlating the pathology of the bone marrow with the clinical and laboratory findings. This has been well emphasized by Dean.[2] I have considered in this paper the group of conditions in which a granulopenia of the peripheral blood is observed with or without local necrotizing lesions in relation to the hematopoietic system as a whole.

The Clinical Picture—The syndrome which Schultz[1] described was characterized by an acute onset, prostration, fever, chills, gangrenous mucosal lesions, and marked leukopenia. Further study has added little to this clinical description except the recognition of milder forms. The leukopenia is due to a great decrease or complete absence of granulocytes. The ulceration may involve the cervix, vagina, penis, rectum or anal area as well as the throat, so there are no constant local lesions. The characteristic blood findings may be observed in the entire absence of necrosis, and the disease is not necessarily fatal. Recovery is not uncommon in both the mild and the severe cases. Numerous cases of recurrence have been described in which there has been a great variation in signs and symptoms with different attacks. Weakness, however, seems to be a striking and almost constant symptom of

granulopenia. Exactly the same clinical picture may be observed in cases in which leukemia is later proved to be present.

All the evidence indicates that the ulcerative lesions are secondary to the decrease in granulocytes and consequent loss of their normal defensive power. Numerous bacteriologic studies have demonstrated organisms of many kinds in the local lesions without any one predominating. Blood cultures made during the height of clinical symptoms frequently give positive findings, but a variety of organisms has been recovered. Local or general infections once established may be an important factor in the final outcome, but it seems evident that bacteria have little to do with the primary injury. In cryptic or idiopathic granulopenia, an overwhelming infection of any type may, however, cause the same picture, but here the primary disease is self-evident.

Etiology—Many different causes of granulopenia have been considered, but bacteria and chemicals have been most prominent. It has long been known that certain drugs, as benzol and arsphenamine will produce a profound leukopenia by a depressing action on the marrow. Usually, however, all elements of the marrow are affected by such agents. Kracke[8] attempted to reproduce the disease in rabbits by the use of various oxidation products of benzene, aniline dyes, and drugs of the coal tar derivatives. He found that benzene given subcutaneously in small amounts showed a selective affinity for the myelocytic tissues with resultant peripheral leukopenia and frequent infection. He suggested that substances which contain the benzene ring should be strongly considered as the cause of granulopenia. Since not infrequently a marked leukopenia has been observed in overwhelming infections, either local or general, numerous attempts have been made to reproduce the condition with organisms recovered from local lesions, or from the blood of patients suffering from the disease, with but little success. While it is true that marked myeloid depression may be produced by certain bacteria, no one organism gives constant results experimentally or is regularly recovered from the affected individuals.

Radiant energy will produce a marked leukopenia, but this can be eliminated as a possible cause in most cases of granulopenia. A blood picture and often clinical findings identical with those of cryptic granulopenia may be observed in splenomegaly, especially Banti's disease, leukopenic leukemia, pernicious anemia, and aplastic anemia. Usually in such cases all elements of the bone marrow are affected, but at times the involvement of myeloblastic tissues is predominant, so that the leukopenia is all out of proportion to the erythropenia and thrombopenia.

The most important contribution to the etiology of cryptic granulopenia has been the proof that certain commonly used drugs, princi-

pally amidopyrine, and especially in drug sensitive individuals, may specifically depress the myeloid tissue of the marrow. Kracke[3] noted that eight of nine patients with granulopenia of undetermined origin had been taking drugs of the coal tar series prior to the onset of clinical symptoms. He was unable to affect the leukocyte count experimentally, however, with such drugs. Madison and Squier[4] were the first to incriminate definitely amidopyrine, especially in combination with a barbiturate as the cause of granulopenia. They found that the onset of granulopenia was often directly preceded by the use of amidopyrine alone or in combination. Several of their patients were known to have a normal blood count or even a leukocytosis before the use of the drug. They also found that a profound granulopenia again developed in two patients, who after recovering from an attack, took a single dose of amidopyrine. Additional evidence that amidopyrine and similar drugs are the most important etiologic agents in cryptic granulopenia is rapidly accumulating.

The Activity and Lability of Normal Bone Marrow—Although all tissues of the body are constantly being torn down and built up, the bone marrow is one of the most active of all. The bone marrow should be looked on as an organ,[5] and one of the largest in the body (about 1500 cc.). The striking activity of the marrow is well shown in its relation to erythrocyte formation. A red cell lives in the circulation from two to four weeks. If we take twenty-five days as the mean span, 1/25 of the entire mass of red cells, or about one trillion erythrocytes, must reach maturity and be discharged from the marrow every day. The life span of the granulocyte in the human is unknown, but it is probably very short—possibly only a few hours and certainly not more than a few days. There are roughly twenty-five billion granulocytes in the circulating blood of a normal adult, so at least from five to twenty-five billion granulocytes must mature and be released from the marrow every twenty-four hours. There is a rapid, continuous process of growth and maturation. Every granulocytosis and every granulopenia represents a disturbance in this normal rhythm. The process of development in the marrow may be conveniently grouped into three stages. The first is the stage of origin. Here the primitive white cell develops from the reticulum cell, and in time becomes a myeloblast, and then an early myelocyte. Multiplication may take place in all four cells but is most active in the early myelocyte stage. Proliferation now ceases, and differentiation of each cell into the mature neutrophil through successive stages of nuclear growth and development follows. The third stage is that of emergence or delivery into the circulation. The circulating stage is short and of little physiologic importance since the white cell functions locally at some point reached by the blood stream rather than in the circulating blood as does the red cell. A

disturbance of the granulocyte may involve any or all of these different stages. It is especially important to remember that to function normally at the site of final localization, the granulocyte must be qualitatively normal as well as quantitatively sufficient. Too little emphasis has been laid on the qualitative changes. After emergence, the granulocytes undergo no further differentiation or change in the circulating blood. Thus, the condition of the cells in the circulation is due to the state of the marrow. Changes in the marrow always precede those in the circulating blood.

The Bone Marrow in Granulopenia—Schultz[1] found a striking absence of myeloid cells in the bone marrow of the patients he described. There was little involvement of the erythroblastic tissue which accounted for the absence of anemia. Other observers likewise report an aplasia of the granulocytic elements of the bone marrow, but further studies have shown, however, that the peripheral leukopenia does not necessarily mean a bone marrow aplasia. Fitz-Hugh and Comroe[6] in nine autopsies found myeloid hyperplasia in more than half. This finding they think confirms the idea of "maturation arrest" previously suggested by Fitz-Hugh and Krumbhaar[7] as the fundamental disturbance rather than myeloid aplasia. Jaffé[8] concludes from autopsy studies in nine cases that the myelocytes bear the brunt of some toxic action on the marrow with evidence of degenerative changes. He found this identical characteristic picture in neutropenia due to salvarsan (2 cases), overwhelming infection with granulopenia (2 cases), and in the so-called idiopathic granulopenia (5 cases). The marrow was active but toxic, so that normal multiplication and maturation either in quantity or quality could not go on. Fried and Dameshek[9] found a great variation in the bone marrow even in constant peripheral leukopenia in experimental granulopenia in rabbits injected with Salmonella suipestifer. Schilowa[10] likewise found a great variation in the bone marrow picture in benzol poisoning in dogs. Some animals showed hyperplasia, others aplasia. While benzol poisoning typically causes a leukopenia and thrombopenia, in some animals there was a leukocytosis and thrombocytosis. These findings are easy to understand when we realize that many agents which destroy in larger doses will stimulate in smaller amounts. Radiant energy is a classic example of this fact. A case of benzol poisoning in a man who had anemia and neutropenia has been reported recently by Anderson[11] in which the autopsy showed hyperplasia of the marrow. Jackson and Parker[12] have studied at autopsy the bone marrow from twenty-five patients who had this disease. In patients dying early in the course of the disease, they found little gross change in the marrow, and no involvement of the red cell series or megakaryocytes. There was a striking absence of cells of the granular series, except stem cells which were plentiful and in

active mitosis. They conclude with Fitz-Hugh and Comroe[6] that "maturation arrest" is an important part of the picture. In patients who survived from eight to twenty days, the marrow was hypoplastic and even stem cells were scarce.

In summary, one may say that there is no characteristic marrow picture in granulopenia except usually, predominant involvement of myeloid cells which are affected both quantitatively and qualitatively. The marrow findings depend upon the stage of the disease and the extent of damage as well as upon the effect of secondary factors, such as infection. In any event, it is evident that the peripheral blood findings result from the marrow disease. It is also evident that the marrow changes are no different in leukopenia due to marrow toxemia caused by known agents than in that due to unknown agents (so-called idiopathic granulopenia).

The Blood Findings in Granulopenia—The one constant blood finding is leukopenia and granulopenia. The total white blood cell count may vary from a few hundred cells to 2500. The lowest number I have seen is 100 cells. The count is seldom higher than 2500 cells during the active stages of the disease. Marked local infections may occur, and there may be a moderately low count while infection may be minimal with an extremely low count. The granulopenia is the predominant change, but in the very low counts there is necessarily a decrease in lymphocytes and monocytes as well as in granulocytes. Patients with extreme anemia and thrombopenia are usually excluded, although almost always some degree of anemia is present. Schultz[1] emphasized the absence of anemia, and this has usually been considered an essential part of the clinical picture. However, with marked myeloid involvement there is almost always some change in the red cells and platelets.

Qualitative changes in such granulocytes as are found in the peripheral blood are striking and have been given too little attention. The circulating granulocytes are seldom normal qualitatively. The nuclei often show pyknosis and other variations from normal in the chromatin-parachromatic pattern. The most striking changes, however, are in the granules and cytoplasm. The granules are decreased in number, vary greatly in size, and show increased basophilic staining. The cytoplasm often shows vacuoles. The cells may be swollen and much larger than normal. As Jaffé[8] has emphasized, such changes are all evidence of some toxic effect on the granulocytes in the marrow.

Classification of Granulopenia—Since I have emphasized that so-called idiopathic granulopenia is only a reflection of bone marrow disease, it is important to have clearly in mind the relation of the different types of leukopenia and granulopenia to changes in the mar-

row. The following classification attempts to correlate the varying clinical and pathologic pictures in cases characterized by peripheral leukopenia:

Classification of Granulopenia

I. ***Granulopenia*** with decrease in erythrocytes and thrombocytes from aplasia or hypoplasia of all bone marrow cells due to:
   1. Infection
   2. Radiant energy
   3. Chemicals as arsphenamine or benzol
   4. Diseases of the spleen as Banti's disease
   5. Unknown causes (idiopathic)

II. ***Granulopenia*** due to mechanical interference with delivery of mature granulocytes in:
   1. Hyperplasia of myeloblastic tissue with leukemia or myeloma
   2. Hyperplasia of erythroblastic tissue in pernicious anemia

III. ***Granulopenia*** due to selective interference with multiplication, maturation or delivery of granulocytes from the marrow by:
   1. Chemicals as amidopyrine and phenobarbital
   2. Allergic reactions
   3. Infection
   4. Radiant energy
   5. Unknown causes (idiopathic)

Illustrative Cases

I. Granulopenia with Decrease in Erythrocytes, Thrombocytes and Myeloid Cells from Aplasia or Hypoplasia of All Elements of Bone Marrow due to:

(a) Sulpharsphenamine—A.E.C., a merchant, thirty-nine years old, received twelve injections of sulpharsphenamine from April to November, 1932. In December, 1932, he was confined to bed because of chills, fever, weakness, and pain in the back. At this time he was very pale and dyspneic. The first blood examination made January 27, 1933, showed 1,100,000 red blood cells, 4,300 white cells, and a hemoglobin content of 20 per cent. No local infections were present. Several blood transfusions were given, and improvement in the patient's condition resulted.

When the patient was first seen in the Cleveland Clinic, March 25, 1933, the examination revealed no findings of significance except for pallor and many petechiae. At this time, the red cells numbered 2,860,000, the hemoglobin content was 44 per cent, and the white cells numbered 2,000. The fragility of the erythrocytes was normal, the reticulocytes were less than 0.2 per cent, and the icteric index was 5. The thrombocytes numbered 10,000, the bleeding time was over 40 minutes, and clot retraction was absent. A differential count of the leukocytes showed 17 per cent neutrophils, 78 per cent lymphocytes, and 5 per cent monocytes. No abnormal white cells were seen. While the patient was under observation, the white cell count fell to 1,250, and there was almost entire absence of granulocytes. After further transfusion, pentnucleotide, and liver

therapy the patient continued to improve and when last heard from, he had returned to work.

In this case there was evident involvement of all elements of the marrow, although as judged by the peripheral blood findings the myeloid tissue was involved out of proportion to the erythroblastic tissue.

(b) Banti's Disease—B.C.G., a boy fourteen years old, during the course of a routine examination six years previously, was found to have a large spleen. He had been entirely well except for poor endurance on exercise. He had been advised to have the spleen removed and came to the Cleveland Clinic for confirmation of this advice.

On examination, there were no significant findings except a spleen which extended down to the crest of the ileum and to the right of the midline above the umbilicus. The Wassermann test gave negative findings and examination of the urine showed nothing of significance. Examination of the blood revealed 4,250,000 red cells, 68 per cent hemoglobin, and 1000 white cells with the following differential count—neutrophils, 53 per cent, eosinophils, 4 per cent, lymphocytes, 36 per cent, and monocytes, 7 per cent. The platelets numbered 140,000, and the icteric index was 5.

The leukopenia was evidently due to the splenic disease and produced no symptoms.

(c) Idiopathic Aplastic Anemia—F.C., a boy fifteen years old, had noticed soreness and bleeding of the tonsils one month before admission, and this was followed by petechiae and weakness. One week later, the neck became swollen, and the gums began to bleed. For two weeks blood had been present in the stools, and for one week in the urine.

Physical examination revealed the patient to be very pale; there were many petechiae over the body, and the gums were bleeding. There was no marked enlargement or ulceration of the tonsils. The spleen was not palpable, and the glands were not enlarged. The temperature was 103°F. Soon after admission, a large mass developed in the jaw which seemed to arise around an abscessed tooth. The spleen became larger, and the high temperature continued. Proctoscopic examination showed a large ulceration in the rectum. One week after admission, consolidation developed in the left lower lobe of the lung, and he died three days later.

The blood count on admission revealed 800,000 red blood cells, the hemoglobin content was 13 per cent, volume index 1.06, and color index 0.81. There were no signs of regeneration of the red cells. The white cell count was 400, with 46 per cent neutrophils, 50 per cent lymphocytes, and 4 per cent monocytes. No abnormal white cells were seen. The platelets numbered 20,000, the bleeding time was 45 minutes, and the coagulation time was 12 minutes (Lee and White method) without clot retraction. Three days before death, the white cell count was only 250.

The autopsy showed the spleen to be normal in size, and there was no evidence of leukemia. The bone marrow in the lumbar spine, sternum and ribs was grossly pale and fatty in the head of the tibia. Sections showed marked aplasia of the marrow with a large amount of fat and sparsely scattered indifferent mononuclear cells. No myelocytes and very few cells resembling granulocytes could be found.

II. Granulopenia Due to Mechanical Interference with Delivery of Mature Granulocytes in:

(a) Leukopenic Leukemia with Angina—M.L.L., housewife fifty-three years old, was first seen February 23, 1934, in the Nose and Throat Department of the Cleveland Clinic. She complained of sore throat which had been present for four weeks. Examination at that time revealed a necrotic, ulcerated area in the right tonsil, with deep excavation and slight cervical glandular enlargement. She had had an active arthritis several months before, and on admission she complained of pain in the left shoulder, but there was no objective evidence of arthritis. The examination was negative except for throat findings.

The initial blood examination showed 3,760,000 red blood cells, a hemoglobin content of 68 per cent, and 1,400 white blood cells with 19 per cent neutrophils, 80 per cent lymphocytes, and 1 per cent eosinophils. No abnormal white cells were seen. The patient was known to have an idiosyncrasy to quinine, but she gave no history of taking drugs which might cause a bone marrow depression. Under observation, this patient's throat lesion healed completely, although she continued to have fever. Several subcutaneous nodes developed, all of which resolved without evidence of active inflammation. Pentnucleotide, injections of liver extract intramuscularly, iron, and blood transfusions were administered. The leukopenia continued, but no immature cells were ever seen. The anemia was progressive, and the last blood count six months after admission showed only 700,000 red cells, 15 per cent hemoglobin, and 1,500 white cell. The white blood cell count was frequently below 1,000, and there was almost entire absence of granulocytes. In many examinations, no immature white cells were ever seen.

This patient died four months after leaving our care. At that time, the leukocyte count was 34,000, and many myeloctytes were present. Autopsy was refused.

This patient evidently had leukopenic leukemia from the onset of her illness, although the diagnosis was impossible from a study of the peripheral blood. No biopsy of the bone marrow was made. The early onset of a necrotic pharyngeal lesion with complete recovery from the local lesion is most unusual.

(b) Pernicious anemia—A.S., a widow sixty-two years old, was referred to the Cleveland Clinic with a diagnosis of carcinoma of the stomach. The physical examination revealed only an evident anemia. The neurological examination gave only negative findings. A roentgenographic study of the gastro-intestinal tract showed no evidence of disease. The test meal revealed achlorhydria. The blood examination showed 2,260,000 red cells, 55 per cent hemoglobin, volume index, 1.35 and color index, 1.22. The white cell count was only 2,000 with 34 per cent neutrophils, 57 per cent lymphocytes, 8 per cent eosinophils, and 1 per cent monocytes. With specific liver therapy, this patient's white blood cell count and other blood findings have returned to normal and have remained normal. The leukopenia here was due to enmeshment of the granulocytes in the hyperplastic red marrow.

III. Granulopenia Due to Selective Toxic Action on Myeloid Tissue in the Marrow By:

(a) Phenobarbital—M.F., a housewife twenty-eight years of age, was first seen in the Cleveland Clinic October 28, 1929. Functional vertigo was diagnosed, and phenobarbital was prescribed. A blood examination made at that

time showed 4,580,000 red cells, 80 per cent hemoglobin, and 6,700 leukocytes. One week later, a maculopapular eruption developed which was diagnosed measles. After a period of two weeks, another marked rash appeared which was first thought to be due to scarlet fever, but was later considered a drug rash. Two months later, the patient was admitted to the hospital, complaining of pain in the ear. At this time, her temperature was 103° F., and exfoliative dermatitis was present, but there was no throat lesion. Later, open sores appeared on the buttocks and on the back. The leukocyte count on admission was 2,400 with 1 per cent neutrophils, 1 per cent eosinophils, 1 per cent basophils, 2 per cent monocytes, and 94 per cent lymphocytes. The red blood cells numbered 3,700,000, and the hemoglobin content was 75 per cent. The white cell count fell as low as 1,000, and a marked anemia developed later. With transfusions and supportive therapy, the leukopenia disappeared, and the red cell count and hemoglobin returned to normal. The temperature was elevated for one month. The skin lesion cleared entirely. An alopecia developed.

Three years later, this patient was again admitted to the hospital for acute abdominal pain, and was given one and one-half grains of phenobarbital. Dermatitis with redness, swelling, and itching quickly developed. At this time the leukocyte count was 22,600 with 96 per cent neutrophils. Later, a reaction to morphine developed after operation, but no blood count was made.

This patient was known to be sensitive also to certain foods and to quinine. Granulopenia and dermatitis developed after the use of phenobarbital. The granulopenia was evidently due to myelotoxicosis, and later the red cells were involved also. At another time, a single dose of phenobarbital produced leukocytosis and a rash.

(b) Amidopyrine with Recurrent Angina and Granulopenia—R.E.H., a physician twenty-nine years of age, was perfectly well until September, 1932, when he had an illness of two weeks' duration which was diagnosed rheumatic fever. The joints were painful for one week, the spleen was palpable, and the attack was followed by generalized weakness for two months. The blood count at that time showed 5,000 leukocytes. In February, 1933, he began to have weakness accompanied by fever and chills. A blood count again showed 5,000 leukocytes. Similar minor attacks occurred twice in March and in early June, 1933. June 11, 1933, following the extraction of a tooth, a high temperature, chills and weakness developed, and this was followed by ulceration of the tongue and throat. The white cell count fell to 1,250, with complete absence of neutrophils. Five injections of pentnucleotide were given, and the blood count returned to normal, and the symptoms disappeared. In October, fever, chills, and weakness again developed. The white cell count fell to 700 with an absence of neutrophils, and the ulceration of the tongue and throat recurred. The patient was given four injections of pentnucleotide without response. On November 10, he had an attack of migraine. Nine days later, the white cell count was 3,100. Following this, fever and nasopharyngeal ulcerations were noticed. At this time, liver extract was given intramuscularly, and the white cell count rose to 6,000, and all symptoms subsided. When he was seen in the Cleveland Clinic, December 15, 1933—fifteen months after the onset of the illness—the red cells numbered 4,635,000, the hemoglobin was 95 per cent, and the white cells numbered 4,700 with 44 per cent neutrophils, 42 per cent lymphocytes, 4 per cent eosinophils, and 10 per cent monocytes.

The patient was not conscious of any drug sensitivity, but he had had migraine for many years for which he had taken allonal, phenobarbital and amidopyrine. Quinine had been used for the joint disturbance. He had been

taking one and one-half grains of phenobarbital twice a month previous to the onset of the illness. In September, he noted that on two occasions, two weeks apart, taking one allonal tablet induced a chill the following day.

The patient had kept a careful blood count record for a long time. After the possible drug etiology was called to his attention, he analyzed the chart in reference to the attacks of migrane and medication. He found that he could date each attack of illness, with and without the necrotic lesions, to the use of amidopyrine or other derivatives. When the tooth was extracted in June, 1933, he had taken 10 grains of amidopyrine and one and one-half grains of phenobarbital.

All drugs have been eliminated. This patient has now been followed for more than a year, and he has had no recurrence of symptoms.

Treatment—The results of the treatment of granulopenia will depend upon the type and extent of marrow damage, the recuperative power of the injured marrow, the seriousness of secondary infection, and the general condition of the patient. The first move in every case is to find and to remove the cause of the marrow injury if possible. Often the cause is obvious. In most cases of cryptic or so-called idiopathic granulopenia, the cause has not been recognized until a short time before the patient appears for examination. This type was formerly considered a uniformly fatal condition, as the use of the terms malignant and pernicious indicate. If the marrow is damaged beyond repair and secondary infections have supervened, the patient is necessarily beyond recovery. It is this type which has become associated in the mind of the clinician with the word agranulocytosis. In the cases reported earlier, we now know that the use of the very drug or drugs responsible for the initial marrow injury often was continued during the course of the disease, thus entirely precluding recovery. The marrow injury occurs in all degrees of severity, so there is no longer any reason to consider it a uniformly fatal disease.

Other than removal of the cause, all therapeutic measures are directed towards improving the general condition of the patient and stimulating the bone marrow to repair and normal activity. From the supportive standpoint, transfusion of blood is a most valuable procedure and should be used in all patients who are seriously ill. Transfusion should be given frequently during the active stages of the disease. Nutritious food and abundant fluids are necessary. Glucose and saline solution should be given intravenously and in large amounts if the patient does not have a sufficient food and fluid intake.

Numerous specific measures stimulating to the marrow have been used. X-ray has been tried but probably is of little value. Nucleotide therapy helps in some cases as is evidenced by the increase in leukocytes following its injection. Since its introduction, we have employed this in the form of pentnucleotide in all cases and have found it of help in some and valueless in other cases. Jackson and Parker[12] recommended

its intramuscular injection in doses of 10 cc. three times a day until the white cell count has been normal for several days. If the count is below 1,000, or the patient is extremely ill, they recommend using from 40 to 50 cc. daily which is administered intramuscularly or in small amounts intravenously. In giving pentnucleotide intravenously, 20 cc. is diluted in 1,000 cc. of isotonic saline solution and given at the rate of 50 to 100 drops per minute.

More recently, intramuscular injections of liver extract have been tried and found to be of value. I have seen several patients who responded to liver therapy after failure of response to pentnucleotide. The liver extract should be given in large doses such as 10 cc. of Lederle's parenteral liver extract each day, or 3 cc. every four hours, and frequent blood counts should be made to gauge the effect.

It is, of course, most important to treat adequately the secondary infections such as the nasopharyngeal lesions. Smears from such lesions usually show spirochetes and fusiform bacilli. For this reason, neoarsphenamine is usually recommended. This is an unwise procedure because of the great danger of causing further bone marrow damage.

The treatment may be summarized as follows:

1. Removal of the cause, if possible, with especial attention to amidopyrine.

2. General supportive measures, such as transfusions, forced fluids, and adequate feeding.

3. Specific stimulating measures for the bone marrow:
   (a) pentnucleotide
   (b) liver extract

4. Treatment of the complicating secondary infections.

Discussion

Granulopenia or agranulocytosis should not be considered a definite etiological or clinical entity. The clinical and marrow picture is one which may be observed in identical form in numerous pathological conditions. The so-called idiopathic granulopenia does not differ clinically or pathologically from other granulopenias in which the cause is known. The condition is idiopathic only in the sense that the cause is unknown. Many such cases have already been explained as due to drugs, and so they are removed from the true idiopathic group.

The granulopenia, which has been emphasized, is in turn due to marrow injury and this, after all, is the most important feature of the disease. The granulopenia is of importance only as it reflects marrow injury, although the loss of the normal protective power against in-

fection explains the secondary infections. The marrow changes are very variable and depend upon the duration of the disease, the intensity of the marrow damage, as well as upon the amount which has been taken of the agent responsible for the marrow damage. While granulopenia as observed in the peripheral blood is always due to marrow involvement, the state of the marrow is not predictable from the blood findings. We should always think of the condition as a primary myelotoxicosis and try to find the substance responsible for the marrow injury. The blood findings are secondary, so the granulocytosis and the angina and other secondary infections are the result of the peripheral granulopenia.

Too much emphasis has been laid on the specific involvement of myeloid tissue in so-called idiopathic granulopenia. While it is true that the involvement of this tissue is out of proportion to the involvement of erythroblastic tissue and megakaryocytes, this is never absolute, and certainly cases in which there is no involvement of red cells and platelets blend into those having a marked depression of these elements. The toxic agents responsible for the condition do, however, have characteristically a selective affinity for white cell-forming tissues. Since the pathologic picture is identical in the myelotoxic granulopenias with known etiology and in those with unknown etiology, it is only a question of finding the toxic agents responsible for the picture in the unknown or idiopathic group. The clinical and pathological picture will vary with the amount and the toxicity of the causative agent as well as with the susceptibility of the patient to the agent; thus, every degree of marrow involvement may occur. The so-called malignant types differ from the mild types only in degree of intoxication and susceptibility of the individual to damage.

The susceptibility of reaction of the affected individual to the etiologic agents is probably the one most important factor in determining the amount of marrow damage. The incidence of hypersensitiveness to drugs in our group is most striking. Large doses of drugs which will injure myeloid tissue may, however, cause a granulopenia in individuals who are not drug sensitive, especially if they are taken over a long period of time. The condition usually, however, represents an unusual effect on the myeloid tissue in a drug sensitive person. The most significant development in relation to the disease is the demonstration that such commonly used drugs as amidopyrine and phenobarbital will produce the disease. This fact well explains the high incidence of the condition in doctors and nurses who are more apt to use such drugs.

The essential nature of the disease is a myelotoxicosis. When one considers the activity and lability of the bone marrow, it is surprising

that the mechanism of white cell formation is not disturbed more frequently. Frequent hypersensitivity to drugs and the common use of drugs which can injure bone marrow explain the increasing incidence of granulopenia. Minor degrees of granulopenia must be exceedingly common, although they are seldom recognized.

There may be any degree of involvement of the marrow at the stage of origin, maturation, or delivery. Autopsy studies concern only the most serious cases. The bone marrow biopsies unfortunately show changes only in the one area examined, usually the sternum, and this is not necessarily the picture in the marrow of all bones. It should be emphasized also that the involvement of the granulocytes is qualitative as well as quantitative. The local lesions are due to a loss of protective power of the neutrophils, and this depends on qualitative as well as on quantitative variations. There may be marked secondary lesions when the total count is not any lower than is frequently observed in conditions such as Banti's disease in which secondary infections seldom occur. Here, while granulocytes may be present, they are unable to perform their normal function, due to some toxic action on them in the marrow. The pathologic findings recorded by Jaffé[8] well explain the condition of such granulocytes as do get into the circulation.

The importance of amidopyrine and similar drugs as the primary myelotoxic agent first emphasized by Madison and Squier[4] now seems well proved. Fitz-Hugh[13] incriminated amidopyrine in one-half of his cases, and Watkins[14] in 13 of 32 cases. It is the most common etiologic agent in our series. Sturgis and Isaacs[15] considered amidopyrine as the cause of the disease in 7 of 9 patients. Three of their patients after recovery were given small doses of the drugs and all again developed granulopenia due to idiosyncrasy to the drug. Smaller series of cases have been reported by others after the drug had been taken for some mild illness preceding the granulopenic syndrome and forgotten by the patient, so necessarily there is a group of cases in which the use of the drug is difficult of proof.

Pepper[16] was the first to call attention to the frequent occurrence of allergy in patients who had idiopathic granulopenia. This is a most important observation as it probably is usually the drug idiosyncrasy which determines the marrow damage by a drug or drugs which have a selective affinity for myeloid tissue, although very large amounts may cause trouble in individuals without drug idiosyncrasy.

Time will probably prove that all true so-called idiopathic granulopenia is due to the toxic action on the marrow of some drug. The list of drugs which will cause such an effect is increasing. Dinitrophenol has been reported in a few instances. It is interesting, as emphasized by Kracke,[3] that all such drugs contain the benzene ring.

Summary

The bone marrow is normally in a very labile state and relatively easily influenced by toxic agents—bacterial, chemical, or physical.

The leukocyte picture as observed in the circulating blood results from the condition of the marrow.

Idiopathic granulopenia (agranulocytosis) is not a clinical entity but a symptom complex in which the fundamental condition is a myelotoxicosis.

The ulceration characteristics of the leukopenic states are secondary to loss of the defensive power of the leukocytes which in turn is due to both quantitative and qualitative changes in the granulocytes.

The granulopenia may be part of a generalized aplasia of the marrow, an interference with delivery of granulocytes, or a specific depressing effect on myeloid tissue.

A classification of granulopenia and illustrative cases of each type is given.

In the so-called idiopathic granulopenia, the common cause is amidopyrine and similar drugs. In a few cases, however, the cause is not evident so the condition is idiopathic but only in the sense that the cause is unknown.

In treatment, the first essential is recognition and removal of the cause. The patient must be tided over by transfusion and other general measures until bone marrow repair can take place.

In some cases, pentnucleotide and liver extract may aid in the repair of the marrow by stimulating the maturating process.

Every patient with granulopenia should be carefully analyzed from the standpoint of possible etiologic factors and the state of the bone marrow.

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SURGICAL PROBLEMS ASSOCIATED WITH CHOLELITHIASIS*

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The surgical treatment of cholelithiasis naturally includes the management of cholecystitis. The etiologic factors in cholecystic disease can only be mentioned here. A vast amount of experimental work has been done on the etiology of gall stones, but this has not greatly altered the conception that there are three main factors, infection, stasis and cholesterol metabolism, which function in their causation.

In discussing this problem, Twiss and Green[1] have contributed a very excellent article on the dietary and medical management of the disease. They made the pertinent statement that a tremendous amount of work has been done on different phases of cholesterol metabolism but so far there is no final agreement as to the origin, function or fate of this material. They feel that if medical therapy is ever to supplant surgery in this field of medicine, it will be necessary to recognize and to correct disturbances in the biliary tract before the calculi are formed.

One question which almost always arises in the surgeon's mind concerns the rate of formation of these stones, and it is possible that cholecystography may lead to more complete information about this phase of the problem. I was very much interested last year while visiting a clinic of Dr. John Finney, Sr., to hear him cite the case of an elderly woman who had acute suppurative cholecystitis with stones. Her condition was such that he did not feel justified in performing cholecystectomy, but did do a cholecystostomy and removed a large number of stones which had packed the gallbladder. This patient made a good recovery, but one year later returned with recurrent acute cholecystitis, and to his surprise he found that the gallbladder again was completely filled with stones.

I have felt for some time that since the advent of cholecystography many of the points which the radiologists formerly taught about gall stones have been overlooked. Often shadows are seen in the gallbladder area which might be mistaken for gall stones unless a differential diagnosis is made. In a comparison of 100 consecutive gall stones with 100 consecutive kidney stones, it has been found that approximately 85 per cent of the gall stones show faint shadows while 85 per cent of the kidney stones show dense shadows. It is also more or less generally forgotten that if the patient is turned on the abdomen when the roentgenogram is made, there is a marked difference in the size of the stones. They appear much smaller when the patient is in the posterior-anterior position than when he is in the anterior-posterior position. The reverse is true of renal calculi. Less emphasis has also

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been placed upon the typical defect, an elliptical, sharply defined concavity, which the gallbladder can produce in the duodenal cap. It is to be pointed out, however, that unless the defect persists in all positions, it may not be of importance, as the duodenum may empty completely if the picture is taken with the patient on the abdomen. With barium in the stomach it is perfectly easy to demonstrate this defect. It is surprising how often gall stones are noted also by the radiologist in the taking of routine roentgenograms of the spine and the kidneys, ureters and bladder. Although the radiologist objects to making barium injections into a colon without a complete roentgenologic study of the gastro-intestinal tract, including a cholecystogram, it is also striking that gall stones are found frequently in cases in which barium studies on the colon are being made.

There are a few special points on cholecystography which might be mentioned. It has been of particular aid in the diagnosis of cases of cholelithiasis without colic, showing negative shadows. Kirklin,[2] with his enormous experience, has stated that ordinarily gall stones are not recognized as such by cholecystography in more than 50 per cent of the cases, but in most remaining cases the absence of any shadow of dye will indicate that the gallbladder is not functioning normally, and in his experience 98 per cent of cases of gall stones have given positive cholecystographic data, indicative of disease or malfunction of the gallbladder. Another diagnostic method which may be of help in some of these cases in which the cholecystogram and physical findings are not typical is the searching for cholesterin crystals by means of the Lyon test. Lahey[3] has recently emphasized the importance of this procedure.

Differential Diagnosis

In considering the differential diagnosis of cholecystitis with stones, one is familiar with the fact that the lesion has been confused with practically every intra-abdominal lesion, especially those of the upper abdomen, as well as the lesions of the right chest, which can not be discussed here. There is one phase of the problem, however, which merits special emphasis. Within recent years, cardiologists have been continually cautioning us about the similarity which may occur between the atypical coronary occlusions and gallbladder disease. It is true, of course, that in the case of the patient who has a typical gall stone colic with sudden severe, agonizing pain in the right upper quadrant, which is referred through to the right shoulder blade, and is followed by residual tenderness and jaundice, there is little difficulty in making a positive diagnosis of cholecystitis with stones. Likewise, the diagnosis of coronary occlusion is just as evident in the patient who has a sudden retrosternal pain, accompanied by peripheral vascular shock, distant

heart sounds and pain in the left shoulder which is followed by a friction rub over the precordium. It is, however, in the group of patients who have the atypical symptoms of coronary occlusion and gallbladder disease that the confusion arises, and particularly if the patient had epigastric pain as the result of the coronary accident. In some of these cases there may even be splinting of the abdominal wall. These patients may also have symptoms of indigestion similar to those seen in chronic cholecystitis. Cholecystograms and electrocardiograms, of course, are of great value in this group of patients, and it may be necessary to have repeated electrocardiographic studies. Unfortunately, however, there is a group of patients with characteristic findings in which neither the cholecystogram nor the electrocardiogram may be of much help. Then, too, these patients are frequently seen in the home when neither of these laboratory aids is available.

There are certain clinical points that might well be borne in mind during the acute attack. First of all, gallbladder disease is much more frequent in women and coronary occlusion is much more frequent in men more than 50 years of age. In the cases of coronary disease, one of the important clinical points is the marked peripheral vascular shock. The patient becomes very pale and has a weak, thready pulse. Another differentiating point is that the patient with acute attacks of gallbladder colic usually is relieved by one hypodermic injection of morphine, while the patient with coronary occlusion practically always requires from one-half grain (1/2 gr.) to two-thirds grain (2/3 gr.) of morphine for relief. It is perfectly logical to assume that if a patient who has had a coronary accident is subjected to laparotomy, the added burden of the surgical procedure will cause a postoperative catastrophe. Hence the question has arisen in some cases of so-called sudden deaths after gallbladder operations, as to whether coronary disease may have been the cause of death, especially in cases in which very little evidence of gallbladder disease was found.

Operative Procedure

In the preoperative preparation of patients, before cholecystectomy, we have learned from bitter experience that many of them should be as carefully prepared for the operation as the patient with hyperthyroidism or the patient with prostatic hypertrophy. They should not only have complete blood studies for bleeding and clotting time but should be given large quantities of fluids along with calcium intravenously, as advised by Walters,[4] and glucose solution and transfusions. In addition to these measures, we are doing more and more liver function tests on these patients. Graham[5] has combined his phenoltetraiodophthalein which is given for the cholecystogram as a test. Here, we have used the glucose tolerance test, in addition to the van den

Bergh and icterus index test, and we feel that these findings add a great deal to the information about the operative risk.

The question has long since been decided that cholecystectomy is, of course, the procedure of choice for cholecystitis with stones. However, that does not mean that the fine operative procedure of cholecystostomy should be completely abandoned, and certainly there are cases, especially in severely ill, elderly patients and in deeply jaundiced patients, in which it is a life-saving measure.

For many years, one of my associates, Dr. W. E. Lower, has done a so-called modified cholecystectomy which is a valuable procedure in selected cases. One is always struck by the very marked edema which occurs in all the layers of the gallbladder in acute cholecystitis with obstruction of the cystic duct, and Dr. Lower, after evacuating the contents of the gallbladder and removing the stones, shells out the mucosa and leaves the serosa intact. Oftentimes, the line of cleavage is very sharply delineated, and the procedure can be very quickly accomplished by blunt dissection. These patients have progressed extremely well after operation. It has the advantage that the mucosa is entirely removed and can not regenerate, and, in addition, the liver bed has not been exposed and contamination of the general peritoneal cavity is reduced to a minimum.

The general technical problems in cholecystectomy are well known and recognizable. There are a few points, however, which are always of interest. One of these is the position of the patient on the table. In my own experience, I have found that it is much easier to expose the gallbladder with the patient flat on the table, rather than to have a kidney support or sand bag under the back. Certainly the recti muscles are much more relaxed, and on the whole, the exposure is easier. The importance of the high incision has been emphasized by many men and is of great help. Whether a gallbladder is removed from above downward or from below upward is, I feel, a matter of the operator's choice. However, I feel quite strongly that too much emphasis has been placed upon the possible pouching of a cystic duct, after it has been ligated, and I have no hesitancy in leaving all of the cystic duct. I feel that there is very little danger of any difficulty in the duct itself, while the danger of injuring the common duct is much greater if it is tied close to the duct. Preferably, the artery should be ligated separately if possible.

After the gallbladder has been removed, and the cystic artery and cystic duct have been tied, the important consideration arises as to whether or not the common duct is to be explored. This old question has recently been emphasized by Lahey,[3] who states that he is exploring the common duct in 46 per cent of his cases. This is, of course, a much higher

percentage than is generally carried out by most surgeons. In this regard, I have been most conservative in exploring the common ducts and fortunately have had little postoperative difficulty. I have, however, followed Moynihan's dictum about carefully palpating the common duct between the index finger and the thumb. In many cases this can be done readily and in the absence of definite indications for opening of the duct, I have used this as a guide. If a patient has (1) a palpable mass, (2) jaundice, (3) a dilatation of the duct or (4) repeated attacks of cholelithiasis with jaundice, the duct should, of course, be opened and carefully explored, and a small catheter, which is directed toward the liver and carefully sutured afterwards, should be inserted.

Without entering into any lengthy discussion on the controversy as to whether or not the wound should be drained, I think there are two important facts that should be mentioned. First of all, I have known some eminent surgeons who have closed the abdomen without drainage following cholecystectomy, and almost without exception these men have discontinued the practice. While the common statement is made that bile peritonitis develops when drainage is not used after cholecystectomy, emphasis has not been placed on the fact that this is a most difficult postoperative complication to recognize. The patient apparently will be progressing satisfactorily after his operation and then suddenly may become severely ill and by the time the complication is recognized it is too late to save the patient's life. Apparently the severity of the patient's illness is dependent upon the factors of the quantity of bile in the abdominal cavity and the time element.

Relationship to Carcinoma

In a discussion of cholelithiasis, the relationship of stones to carcinoma of the gallbladder should be mentioned. In our own series of cases, 79 per cent of the cases of carcinoma of the gallbladder have been associated with gall stones. Graham has pointed out that primary carcinoma of the gallbladder is much more frequent that is generally supposed, and that it constitutes between 5 and 6 per cent of all cases of carcinoma. The history of these patients is that a fairly high proportion of them report attacks of typical gall stone colic, and in the case cited here, the patient had a typical attack of gall stone colic a few weeks prior to the operation, at which time the cancer was discovered. The prognosis in these cases of malignant disease of the gallbladder is, of course, extremely poor, and in our own experience these patients have lived for only a few months after the operation.

In Graham's very excellent resumé of the subject, he points out some very pertinent statistics. In the reported series, from 69 per cent (Musser) to 100 per cent (Janowski) gall stones have been found

accompanying carcinoma of the gallbladder. From the evidence cited by other writers, it would seem that the carcinoma has developed after the formation of the stones. Graham further states that 8½ per cent of all cases of stones in the gallbladder have been associated with carcinomas, and he points out that it brings up one phase of cancer prevention which must be emphasized, and the surprising statement that one person in twenty-five with gall stones will have a carcinoma of the gallbladder.

This brings up the question as to the significance of the so-called silent gall stones and how these patients should be advised by the surgeon. It is always interesting that patients who have so-called silent gall stones have been subjected to roentgen examination for vague gastro-intestinal symptoms of some kind, and the whole question about the operability of these patients depends entirely upon the degree of discomfort which they are suffering. A certain number of these patients do obtain relief by medical measures after the correction of other gastro-intestinal complaints.

With the enthusiasm about foci of infection, the gallbladder has naturally come in for a great deal of consideration. I think it is only fair to state that the results have not been in any way comparable to the results obtained from removing foci of infection in the teeth, tonsils and sinuses, and that, after all, the chief benefit from removing the gallbladder has been for the relief of epigastric pain and associated gastro-intestinal symptoms.

Another question that a surgeon very frequently has to answer is concerning the prevention of attacks of gall stone colic. I have seen a good many patients who have had typical gall stone colic and have advised immediate operation, but they, for one reason or another, wanted to delay the operation. This whole subject is covered most admirably by Twiss and Green.[1]

It is well known that many patients have an attack of pain after the ingestion of a large meal, particularly at night. Dr. John Phillips used to advise these patients to take frequent feedings, following a modified Sippy routine. Although theoretically the ingestion of large quantities of milk and cream would be contraindicated, these patients obtained relief. These dietary measures would probably be of little value in patients who have gall stones, inasmuch as it has been shown that the cholesterol content of the blood is very difficult to reduce by dietary measures. The foods which are rich in cholesterol, of course, are eggs, brain, butter, goose, duck and liver. I have had some patients who insist that they get relief from some of the proprietary bile salts tablets. These may be objected to on the ground that so many of them contain

mild laxatives such as phenolphthalein and cascara, and patients object to the cathartic action.

When one analyzes the accepted contributing factors in cholelithiasis including (1) biliary stasis, (2) infection, (3) disturbances in biliary excretion, (4) cholesterol metabolism, (5) obesity, (6) pregnancy, one is struck by the fact that the problem is complex and that the solution must be worked out separately in each individual case.

Conclusions

The variety and complexity of the etiologic factors, together with the fragmentary knowledge concerning them, makes the medical treatment of cholecystic disease difficult, if not impossible. Hence, at present, the emphasis must be placed on the surgical management of the disease, which can only be improved by more careful attention to the details, such as individualization of each case, extreme skill in the differential diagnosis, which includes accurate interpretation of clinical, laboratory and roentgenologic findings, careful preoperative management and scrupulous care in the surgical technique.

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ALLERGY IN CHILDREN

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We wish to report our observations in a study of 203 cases of clinical allergy in children whose ages varied between 8 months and 15 years. These patients were seen in the Department of Allergy from January 1, 1934, to November, 1935. Although follow-up observations have not been obtained in a small number of these patients and another group has been under allergy control for too brief a time to evaluate the results of therapy, these cases have been included because of points of interest in the histories and clinical findings.

The Approach to the Study of the Allergic Patient

The allergic states have been classified with a view to presenting the outstanding clinical features of each problem. Allergic manifestations are numerous, due to the diversified phenomena occurring in many organs, and the fact that the majority of patients present multiple evidences of an allergic condition. We classified our cases in three groups—respiratory allergy, gastro-intestinal allergy and cutaneous allergy, and attempted to establish a working plan for the diagnosis of definite clinical states.

The approach to the diagnosis of an allergic state can be followed in a very definite manner.

Personal History—Family History—Allied Conditions

One cannot help but feel that the clinical history is the most important of all the procedures in the diagnostic survey. Through this, one may first obtain knowledge as to whether or not the patient is an allergic individual. Such information is strengthened by a close inquiry regarding a family history of allergy, and in a large percentage of our cases, a family history has been elicited through persistent effort, interest and coöperation of the patient. The history must be very complete, not only in regard to the suspected allergic state, but any condition of the system that may alter the patient's state from that of normal. Failure to evaluate the importance of associated disorders results in poor clinical relief; this is particularly true in the presence of metabolic disorders, glandular dysfunction, focal or systemic infections. In taking the history, emphasis must be placed not only on environmental factors, dietary habits and modes of living, but inquiry must also be made regarding the ingestion of unsuspected, apparently harmless medication.

Physical Examination

In our cases, a complete physical examination is made routinely. This consumes only a short time and occasionally some further light is

thrown on the problem. Special examination can be advised only after a complete history has been taken and a physical examination has been made. The laboratory procedures we employ routinely are a Wassermann test, estimation of the blood sugar, complete blood counts and urinalysis. Other tests are made which are indicated by the history and physical examination. If there is any evidence of the presence of an infection, a red blood cell sedimentation rate is indicated. This often gives further clues as to whether a low-grade infectious process is present or one that is due simply to a hypersensitive reaction. In cases of bronchial asthma, a nose and throat examination, and a roentgenogram of the chest are always indicated. Often, we find that a hay fever patient apparently is completely immunized against the suspected allergen, but has symptoms which are influenced by mechanical barriers such as a markedly deflected septum, a spur or polyp, or an old sinus infection. We do not concur with the opinion of many workers in the field of allergy that correction of these conditions should not be carried out, but we believe that mechanical defects in the nose and throat can prevent satisfactory clinical results. It is obvious that the patient must be assured of coöperation between the allergist and the otolaryngologist. When the clinical history indicates disorders of metabolism, the basal metabolic rate should be determined. In patients with migraine and gastro-intestinal disturbances or in the more rare genito-urinary problems, a more complete study is indicated. We do not feel that a diagnosis of allergy should be established in any case until the possibility of organic lesions has been excluded.

Tests for Allergy

From the foregoing discussion, it is obvious that we consider allergy tests as only part of the investigation of the patient's problem. *Each patient must be individualized.* It should not be inferred that tests are carried out in an incomplete manner, but several methods of testing may necessarily be used in the same patient. In the majority of patients, the scratch method is employed first, but if sufficient information is not obtained, or if the clinical history cannot be correlated with the results of the tests, further testing by the intracutaneous method is indicated. The intracutaneous method is that used by the majority of allergists today. The passive transfer method has not gained popular approval as a common procedure, but the indications for its use are many: in children in whom the physical and mental shock from direct testing is great, in patients with eczema where lichenification of the cutaneous surfaces is so marked as to render sites for testing unsatisfactory, in the acutely ill patient, and in cases where a hypersensitive reaction of the skin is noted to every substance applied, as demonstrated in some

cases of urticaria. We have used the passive transfer method on an average of one or two allergy problems daily, and we consider our clinical results to be more satisfactory than those secured by direct methods of testing.

Through these three methods of testing—scratch, intracutaneous and passive transfer—allergens can be identified in the majority of cases with consequent good clinical results. In conditions such as migraine, gastro-intestinal allergy, cutaneous lesions and less frequently the ocular and respiratory conditions where food allergy is suspected, and when skin tests have failed to give satisfactory results, further methods of investigation are employed. The digestive leukocyte response, the elimination or trial diet and food diary lend further aid in the diagnostic survey. Emphasis should be placed upon the necessity of patch testing with ingredients of proposed local medication, this being particularly important in cutaneous and ocular allergy. Not infrequently, patients have returned with an involvement which was more severe than that prior to admission, and this was due to a hypersensitive reaction to drugs used locally.

Routine testing with bacterial vaccines often throws light upon a patient's problem, particularly where chronic focal infection is encountered or has been removed. Included in the allergy tests are bacterial vaccines of standard type, such as the strains of streptococcus, staphylococcus, micrococcus catarrhalis, influenzal and the gonococcus filtrates. Routine tuberculin tests are also done with the Mantoux method in any patient where tuberculin sensitivity is suspected. The tests are made with strengths of 1:100,000, 1:10,000, 1:1,000 and 1:100 as is indicated in each individual case.

After taking the allergic patient's history, making the physical examination, laboratory tests, and allergy tests so that we have available information as to the causes of his symptoms, only 50 per cent of the problem has been solved. In our experience, the greatest cause for failure to obtain reasonable clinical success in patients who are definitely allergic is not due entirely to inadequate investigation, but to the failure of the physician to convey to the patient the understanding of allergic reactions, of allergenic substances and what is to be done about them. This phase of the program demands time and detail on the part of both the patient and the physician. The patient should be acquainted with the fact that his problem has been covered from every viewpoint, and we have made a policy of giving not only complete verbal instructions to the patient, attempting to educate him in regard to the meaning and procedure of allergic study and thought, but also to give complete written instructions. A satisfactory allergy regimen and control can-

not be accomplished unless this policy is strictly adhered to. The average time required for instructing patients is more than that consumed in taking the history and making the physical examination.

Allergens which Can Be Avoided or Eliminated

As a rule, common inhalants with the exception of pollens can be avoided unless the patient is extremely sensitive, and in such instances one must resort to further measures.

In regard to the diet—only simple elimination is necessary, and this is particularly true of every patient, whether he be an adult or a child. In substitutions in the diet, special attention must be given to assure a diet that is both adequate and nutritious. We employ not only the physician's knowledge of this, but also the assistance of our Dietetic Department. In these patients, added vitamins A, B, and D and calcium are of distinct value, not only because they insure against disturbance of diet where major foods are removed, but some beneficial influence to the general physical well being may be derived. The length of time that foods must be avoided in the diet is dependent upon the individual patient and his symptoms. It is reasonable to state that no food which has definitely been proven to be the specific factor should be returned to the diet in less than six months. The program to be followed in each particular case can be determined only by experience.

Allergens which Cannot Be Avoided or Eliminated

Sensitivity to pollens of trees, grasses, weeds and occasionally to pollens of flowering plants necessitate desensitization. It is recognized that pollen hay fever or asthma or infrequently encountered conditions due to pollen sensitivity can be adequately treated by the perennial method of desensitization. It is necessary to have a thorough knowledge of the patient's problem and to continue therapy over a length of time sufficient to render the patient immune to the offending substances.

House dust sensitivity in a number of cases, particularly in chronic respiratory and ocular conditions, demands special consideration. We do not advise house dust desensitization in many patients, but those who are treated obtain good clinical relief. The necessity of desensitizing the patient to house dust can be determined by eliciting a careful history of symptoms on exposure to dust and by judging the degree of skin reaction to house dust antigen.

Occasionally, we encounter allergic patients with ocular, respiratory and cutaneous conditions which require desensitization to one or more of the inhalants—orris root, feathers, animal hairs, silk, kapok and cottonseed. We have used this therapy in several instances and have obtained consistently good results. One point concerning desensitiza-

tion therapy which should be emphasized is that symptoms or signs of too great local reaction should be avoided and certainly any symptoms or signs of systemic reaction should be avoided. It is obvious that signs and symptoms of systemic reaction are evidence of shocking the tissues and not stimulating immunity. This particular principle has a counterpart in that it renders any type of desensitization treatment a long, tedious process. With desensitization therapy, it is necessary to treat the patient at least six months and preferably twelve months, eighteen months, two years or longer.

In patients with pollen hay fever, the therapy may necessarily be instituted for greater lengths of time. Encouraging results are noted in from 80 to 90 per cent of patients who have received desensitization therapy.

In the majority of patients, multiple skin reactions are present. By correlating the results of the tests and the clinical history, the examiner often has difficulty in evaluating the importance of the allergens to which the patient is sensitive. It is often true that no single outstanding allergic reactions appear. In all patients, the substances to which the patient shows a definite, positive reaction by allergy tests should be eliminated or avoided as thoroughly as possible. Elimination of all offending allergens demonstrated by skin tests will result in a strict routine. It is advisable to establish such a regimen and after clinical relief has been obtained for a definite period of time, to attempt a more liberal type of management. The patient who experiences clinical relief needs no additional stimulus to encourage him in the study of his problem.

RESPIRATORY ALLERGY

Seasonal Hay Fever

Fifty-five patients with seasonal hay fever have received complete allergy investigation, and the majority of these, 51, were tested by the direct, scratch and intracutaneous method. Passive transfer was used in four cases. The ages of these patients ranged between 2 and 15 years, with an average age of 10 years. A history of allergic disease in the family was elicited in 35 or 63 per cent of the patients, and in the majority of those giving a positive family history, both the maternal and paternal branches of the family showed evidence of considerable allergic disease.

The symptoms in these patients were those typical of seasonal hay fever—sneezing, watery nasal discharge and nasal fullness and obstruction, burning and smarting of the eyes, lacrimation, itching of the palate and pharynx.

The average duration of symptoms was three and one-half years. Although the majority of our patients have had a fall type of seasonal hay fever, the routine skin tests have included extracts of tree and grass pollens as well as extracts of the weed family or group. We have found that, although only mild symptoms may be present in the spring or early summer, reactions to the tree and grass pollen extracts will be noted in a number of subjects. Because of multiple sensitivity, results will not be satisfactory if only the weed type of pollen antigens is used in the therapy of these patients. The treatment for each individual is based upon the history and upon the results of complete pollen tests.

During the past three years, we have made daily pollen counts from early April until after a heavy frost in the fall, and we have found this to be helpful, not only in the regulation of dosage of the extract used in treatment, but also as an aid in the explanation of any unlooked for symptom during the hay fever season.

Associated allergic conditions were noted in 57 per cent of these cases, and in 32 per cent, associated conditions other than those of allergic origin were found to be present.

Physical examination in these cases revealed the typical findings of seasonal hay fever. Laboratory work in most of the 55 cases was routine, and the significant features revealed by these procedures was that 26 of the 55 patients had a blood eosinophilia which varied from one to 30 per cent. In two cases in which other associated states indicated a metabolic disturbance, the basal metabolic rates were minus 29 per cent and minus 32 per cent.

In the treatment of these patients, perennial desensitization and adherence to an allergy regimen were carried out in 43 cases. In four patients, the allergy regimen alone without pollen therapy was considered advisable and adequate for satisfactory control. Eight of the total number of patients received no treatment, either because of lack of coöperation or because the condition was not of such severity to warrant strict therapeutic measures.

Several of these patients received treatment under our personal supervision, but the majority have had equally as good results under the care of their family physician who coöperated with us.

Of the group of 55 cases, 15 patients or 54 per cent secured results that can be classified as excellent; 12 or 42 per cent had good results and one or 4 per cent had fair relief. None failed to show any improvement. We received no coöperation in seven of these 55 cases, the treatment either being refused entirely or not conscientiously applied. Twenty of our patients have been treated for too short a length

of time to evaluate the results, or follow-up observations have not been obtained, so that the results in these cases can only be classified as questionable.

In conclusion, we feel that of those patients who have received adequate treatment and have given conscientious coöperation, 96 per cent have shown excellent or good results.

Seasonal Hay Fever and Asthma

In this series of cases only those have been included in which bronchial asthma of a seasonal type was the outstanding symptom. A distinction has been drawn between those patients who experienced attacks of asthma chiefly in the pollen hay fever seasons, those who experienced mild attacks at intervals throughout the year, and those patients who had perennial asthma as the outstanding symptom, but who also had a mild seasonal aggravation due to pollen sensitivity. Eighteen cases of the latter sort are presented in the summary of 42 cases with perennial bronchial asthma.

The observations made on 12 patients with the outstanding symptoms of seasonal asthma due to pollen sensitivity are presented here. Although these patients had symptoms which appeared only in the pollen season, they were thoroughly investigated from the allergic viewpoint, and a strict regimen was enforced in all cases. The average age of these 12 patients was 9 years. Six patients or 50 per cent of the total exhibited associated clinical manifestations of allergy, while four or 33 per cent exhibited clinical states not related to allergy—one patient had a deviated nasal septum, one had a colloid goiter, one had Fröhlich's syndrome, and in one case a diagnosis of glandular tuberculosis was made.

A positive family history of allergy was elicited in nine or 75 per cent of the cases. The average duration of symptoms had been 5 years. The symptoms were those typical of hay fever and demanded medication for relief (usually ephedrine orally and often adrenalin subcutaneously).

Roentgenographic studies of the chest were made in the majority of cases and in one patient a roentgen diagnosis of questionable pulmonary tuberculosis was made. Eosinophilia was noted in six cases or 50 per cent; the average eosinophil count was 8.

Allergy tests were made routinely by the scratch method and were supplemented by the intracutaneous or passive transfer method as the individual case demanded. Complete tests by passive transfer were carried out in three subjects. The average number of proteins tested

in each patient was 150, except in the case of those tested by the passive transfer method.

Of the 12 patients in this group, one refused the advised course of therapy, and we were not able to secure follow-up observations on two others. Of the remaining nine, six or 66 per cent secured excellent relief, two or 22 per cent noted good results, one evidenced fair results and none was unimproved. Therefore, excellent or good results were noted in eight of the nine patients or 88 per cent. Every patient in this series is continuing therapy as originally instituted. It is interesting to note that one patient, a girl aged 12 years, received four or five injections of adrenalin daily over a period of from three to four weeks each ragweed season. She suffered complete exhaustion at the close of hay fever season and a loss of 15 to 20 pounds in weight as the result of her illness. Following treatment this patient found it unnecessary to use adrenalin; she had no asthmatic attacks, and the results secured can therefore be classified as good.

Perennial Allergic Rhinitis

Of 514 allergic patients seen in a six-month period in 1933, 137 or 26.9 per cent had perennial allergic rhinitis and bronchitis. These patients were of all ages. In a survey of 203 allergic children seen in 1934 and 1935, 41 or 20.2 per cent presented the major clinical manifestations of perennial allergic rhinitis and bronchitis. These figures show a striking similarity between the incidence of perennial allergic rhinitis and bronchitis in the adult and in the child. Thirty cases in which chronic nasal allergy was the dominant symptom are reviewed in the following discussion.

A carefully elicited history reveals the following symptom-complex to be fairly typical. Symptoms of nasal congestion, sneezing, nasal discharge of serous or mucoid character, postnasal dropping, and often dull frontal headache are noted. Sneezing is not as prominent a symptom as is nasal congestion or nasal obstruction. Eyelid or bronchial symptoms may be present to a lesser degree. Just as pollen allergy has a distinct seasonal variation, these patients experience a definite aggravation of their symptoms during the fall, winter and spring months. In this section of the country, climatic conditions are unfavorable to this group of patients. To all practical purposes, there is no sunshine, out-of-door exercise is curtailed, and contact with house dust due to our heating systems is more imminent; furthermore, infectious colds are more prevalent, and these patients as a rule, contract more colds than the average child. Symptoms resultant from physical agents such as changing temperature, cold wind and wet feet, are evidenced by

the sensitive mucous membranes and are noted in a large percentage of patients. The symptoms are not constant, but vary from day to day or week to week, and the patient never gains a normal state of nasal breathing. Varying mild attacks of bronchitis and asthma were noted in a small percentage of patients and a few patients exhibited mild pollen sensitivity with aggravation during the hay fever season. Cases where definite sinusitis of a purulent nature was demonstrated were not included in this series. Intranasal surgery had not been performed in these patients, but tonsillectomy and adenoidectomy had been performed in the majority of cases.

The average age of the patients in this series was 10 years. Positive family histories of allergy were obtained in 20 or 67 per cent. Associated clinical manifestations of allergy, which were noted in 19 or 63 per cent of the patients, were hay fever, eczema, urticaria, gastrointestinal allergy and bronchial asthma. Associated findings which were not a part of the allergic state in 16 or 53 per cent were malnutrition, obesity, deviated septa, otitis media, hypometabolism and hypertrophied tonsils and adenoids.

The average duration of symptoms was three and one-half years and the symptoms in the majority of patients were typical of this condition. The signs on physical examination were typical of chronic nasal allergy—swelling of the turbinates was an outstanding feature. Transillumination of the sinuses revealed dimming in a number of patients; irrigations revealed no purulent material. Other physical findings not a part of the allergic state have been noted above. Laboratory studies revealed eosinophilia in 16 or 53 per cent of patients, the average eosinophil count being 5 per cent. A basal metabolic rate of minus 18 per cent was noted in one patient. No positive x-ray studies of the chest were noted. The red blood cell sedimentation rate was normal in the cases where such study was made.

Allergy tests were carried out according to the indications in each individual problem. Seven or 23 per cent were investigated for allergy by the passive transfer method, 60 to 80 tests being made in each instance.

Allergy regimens based upon the results of the allergy studies were instituted in all patients. Results of allergy control could not be evaluated in 13 patients due either to failure to obtain complete follow-up observations, or the period of the allergy regimen was too short. Of the remaining 17, five patients or 29 per cent obtained excellent relief; eleven or 65 per cent obtained good relief, and all patients noted fair results. Of the 17 patients observed over a sufficient length of time to

evaluate results, 16 or 94 per cent obtained good or excellent relief. Results of allergy control in this group of patients have been most encouraging.

Perennial Allergic Rhinitis and Bronchitis

Recurring attacks of allergic bronchitis without asthma is recognized as a common problem in children. A diagnosis of infectious bronchitis had previously been made in many of these cases, but why these had been diagnosed as infections is not clear. Possibly the fact that the symptoms occur chiefly in the fall, winter and spring seasons influenced the choice of diagnosis. The therapeutic procedures employed range from the use of tonic measures such as cod-liver oil to the more drastic surgical measures in the hands of the otolaryngologist. The case histories support the contention that these measures are of little avail in the average patient; however, we do not see the patients that respond to such therapeutic measures.

A family history of bronchitis was noted in the majority of patients. It is interesting to note the frequent occurrence of croup and other forms of laryngitis in this group of patients as revealed by the histories. Tonsillectomy and adenoidectomy had been performed on two patients.

An analysis of symptoms in the patients with rhinitis and bronchitis presents a typical picture. A child enjoys fair health during the warm summer months, but after entering school in September, he fatigues easily, and with first weather change of any note, coryza develops as well as some pharyngitis and within 48 hours, there is an irritating, non-productive cough. Systemic symptoms other than malaise are not common; fever may appear in the first 72 hours, but it is usually present only until the fourth or fifth day and seldom longer than the first week—in a number of patients, the course is afebrile. The nasal symptoms persist, with nasal congestion, nasal obstruction, and mucoid nasal discharge. A dry, irritating cough, usually non-productive, continues. If sputum is noted, it is only mucus. The course of symptoms is protracted, the usual duration being three to four weeks. The appetite is variable, inconstant, and at its best, is only fair. The child recovers slowly, is permitted activities, is noticeably fatigued, and in a few weeks, similar series of symptoms develop, and so this sequence of events is repeated throughout the winter and spring months. Our patients had suffered an average of four attacks each winter.

The question of infection is immediately raised. In two of our patients, questionably infected tonsils were present, and one patient had signs of a sinusitis. Glandular tuberculosis must always be considered; peribronchial adenitis following the acute infectious diseases

of childhood must likewise be excluded and other possible infectious influences should be given every consideration.

An analysis of the findings in 15 patients with typical, severe, allergic rhinitis and bronchitis discloses some interesting facts. The average age of the patients was nine and one-half years. A family history of allergy was elicited in 11 or 73 per cent, and the average duration of symptoms was three and one-half years. Associated clinical manifestations of allergy, namely seasonal hay fever, eczema, urticaria, and gastro-intestinal allergy, were noted in 10 or 67 per cent. Other association conditions were exhibited by 5 or 33 per cent, two patients had questionably infected tonsils, one exhibited signs of sinusitis, one had definite malnutrition, and one had progressive high myopia. A roentgen diagnosis of glandular tuberculosis had been made in three instances.

The physical findings in all patients were those typical of nasal allergy. Roentgen studies demonstrated fibrosis at the hilium of the lungs in the majority of patients. Laboratory studies, other than x-ray, demonstrated secondary anemia in one patient. Eleven patients or 73 per cent, had blood eosinophilia, the average count being 3.6. The red blood cell sedimentation rate was increased in the one patient with sinusitis. Mantoux tuberculin tests were made in all patients, and the results were negative in all except one.

Allergy tests were performed by the scratch, intracutaneous, and passive transfer methods. Because of age, it was deemed advisable to do allergy tests by the passive transfer method in seven patients, or 47 per cent. Tests were made for bacterial antigens, either autogenous or stock as the individual case demanded.

Of the three patients in whom roentgen examination gave evidence of glandular tuberculosis, two received deep x-ray therapy, and the third was followed by an added rest regimen. All patients followed a strict allergy regimen based upon results of allergy studies, and generous quantities of vitamins A and D were administered. Calcium, iron and, occasionally, iodides were employed as the individual case demanded and this therapeutic routine has been continued up to the present time.

Of the 15 patients, we were unable to obtain a follow-up observation on four and of the remaining eleven, seven or 64 per cent obtained excellent relief with complete alleviation of symptoms; four patients, or 36 per cent, experienced good relief. There were no unimproved cases. To sum up, allergy investigation and control gave good or excellent relief in eleven patients who had suffered recurring attacks of allergic rhinitis and bronchitis for a period of three and one-half years.

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Perennial Bronchial Asthma

Bronchial asthma presents one of the interesting phases of the study of allergy in children. The majority of patients who presented themselves for study were found to have had asthma over a long period of time. The symptoms had been typical, the attacks had been severe, and the usual type of medication had been used without any longer giving symptomatic relief. Often the patient had been submitted to surgery without relief and in the majority of patients the symptoms had only been intensified. Allergy investigation had been neglected or inadequate.

Our series includes 42 children with perennial bronchial asthma. The average age of these patients was nine years. Twenty-two patients, or 53 per cent, had other associated allergic manifestations. Ten of the 42 patients had other associated states; eight of these had tonsils which were questionably infected in a few and apparently normal in the others; one had a definite sinusitis; and one had contracted undulant fever 4 months previously which aggravated the asthmatic state.

A family history of allergy was positive in 35 cases or 84 per cent. The average duration of symptoms was 5 years, and the symptoms were typical. In practically 100 per cent of the cases, an allergic rhinitis was associated with the condition. The asthmatic attacks in every case were becoming increasingly frequent and severe.

Physical examination revealed questionably infected tonsils in eight patients, sinusitis in one; signs of a febrile disease which proved to be undulant fever in one; typical signs of rickets in one, and various states of malnutrition in three.

A roentgenogram of the chest was made in the majority of patients and in eight, the findings were interpreted as puerile tuberculosis. The tuberculin test using the Mantoux method, (0.01 mg. tuberculin, 1-1,000 dilution) gave a negative skin reaction in all these patients. The red blood cell sedimentation rates were normal, indicating the absence of any infectious element. Progress roentgen studies at three, six and twelve month intervals following control of allergy showed a clearing of the findings that had been interpreted as tuberculosis. The only method of therapy used was control based on the results of the allergy studies. The difficulties encountered in interpreting x-ray studies of the chest in children suffering with respiratory allergy is significant of the necessity of close correlation of clinical history, physical findings, and laboratory and allergy studies before a definite diagnosis is established.

Laboratory findings disclosed that 35 patients or 84 per cent had blood eosinophilia, the average being 6 per cent. Questionable mild

secondary anemia was present in only a few patients. One patient with undulant fever had a strongly positive agglutination test and a very marked skin reaction to 0.05 cc. brucellin vaccine administered intracutaneously.

Allergy tests were carried out by the scratch, intracutaneous and passive transfer methods. Quite often, the problem necessitated the use of all the methods. In 18 patients, where seasonal aggravation was noted and pollen sensitivity was demonstrated, the scratch method was employed routinely, and was followed by intracutaneous or passive transfer methods as the individual case demanded. The average number of protein substances for which tests were made varied between 110 and 160. The passive transfer method was used completely in 18, or 43 per cent of the patients.

The results of the allergy tests and a correlation of the findings with the clinical history indicated a multiplicity of reactions. Definite seasonal aggravation of symptoms during the tree, grass, and weed pollen seasons had been noted by 18 patients. These patients were advised to institute the perennial method of desensitization and followed this advice. Occasionally, patients with marked reactions to epidermals and miscellaneous inhalants which could not be completely avoided were given desensitization therapy. Bacterial sensitivity was rarely encountered as a major factor; hence, bacterial vaccine therapy, either with autogenous, pool, or stock vaccines, was carried out. A strict allergy regimen was instituted in all patients. Vitamins A, B and D, calcium, iron and iodides were prescribed as the individual case demanded. Routinely in the past year, we have employed generous doses of calcium and vitamin A and D in all patients with bronchial asthma. The value of this procedure has not yet been determined.

The results secured in the 42 cases are as follows: In eight patients, or 19 per cent, the allergy regimen has either been instituted for too brief a time to evaluate results, or follow-up observations have not been available. Seventeen or 50 per cent obtained excellent results; 12 or 35 per cent obtained good results; 3 or 9 per cent noted fair improvement; one patient was unimproved. This particular patient had suffered from asthma since infancy and had a great deal of bacterial infection within the bronchial tree and a degree of pulmonary emphysema which was quite marked for a child of 10 years. In one patient, no coöperation could be obtained. In spite of this, a very complete study of the patient was made, and the results appeared promising. To sum up, excellent or good results were obtained in 85 per cent of the sub-

jects and only one patient failed to show any definite, satisfactory degree of improvement.

Nasal Allergy and Sinusitis

The association of allergy and infection in the nasal sinuses has been recognized by many workers. Today we accept the dictum that success of treatment depends upon the recognition and control of both the infection and the allergy. The successful approach to this group of patients includes a thorough investigation for allergy and a regimen based upon the results of such studies before any surgery is advised. Likewise, continuance of the strict allergy routine following surgical procedures is imperative. Swollen, boggy, edematous mucous membranes due to allergic reaction prevent proper healing of tissue following operative intervention, make drainage from the sinuses impossible, and render local tissue vitality and resistance a complete failure. In the Department of Allergy and Otolaryngology, we have seen many patients who had allergy associated with sinusitis, and who had had repeated intranasal operations and radical surgical procedures, all of which resulted in failure to relieve the symptoms. The late Dr. William V. Mullin presented the case summaries of a few of these patients whom we have seen.[1] The remarkable results obtained following institution of an allergy regimen, and conservative, operative measures, if any at all were considered necessary, brings forcibly to the attention of every otolaryngologist and allergist the necessity for careful consideration of each phase of this problem and its influence upon the individual case before methods of treatment are enforced.

By what means can one determine the association and relative influence of allergy and infection? Only through careful evaluation of the history, a complete physical examination, special examination of the nose and throat, laboratory studies both of the blood and nasal secretions for eosinophilia, and interpretation of complete allergy tests can one determine the presence or absence of allergy in these problems. As in every allergic state, the careful history is the most important of the diagnostic measures. Not only a personal manifestation of an allergic state, but the eliciting of a strongly positive family history strengthens the contention that the suspected subject may have allergy. A family history of allergy has been obtained in a high percentage of these patients. The personal history usually discloses the story of frequently recurring and protracted colds since early childhood, which improve in summer and are aggravated in the winter, with poor response to routine therapeutic measures. Then follows the history of an acute infection, obstruction, purulent nasal discharge, local treatments, irrigations and finally surgery. In spite of repeated surgical measures

and local therapy, the symptoms continue without clinical relief. This history is typical for the patient who presents himself with allergy and infection and suggests to the examiner that he is not dealing with infection alone. We have found that the patient with nasal allergy has a stormy and protracted convalescence following nasal surgery, owing to the previously marked edema of nasal membranes, and consequent poor drainage.

Laboratory tests are indispensable. Roentgen studies of the sinuses are often misleading—the clouding of sinus areas, as shown on the x-ray may be due to infection or to a thickened edematous membrane which is an expression of allergic reaction. Only through evaluation of clinical history, physical examination and the results of laboratory and allergy tests can roentgen studies be interpreted. Study of nasal secretions for eosinophils is a routine procedure with many workers, but it should be remembered that such a finding may be changed in cases where an infection is superimposed upon allergic tissues. Purulent secretions may obscure local eosinophilia. Allergy is a systemic state with local expressions in many organs. We have relied upon studies of blood for eosinophilia and have found this test to give findings consistent with the clinical findings in about 50 per cent of the cases. Repeated examinations of the blood disclose a higher percentage of positive findings. Blood eosinophilia is inconstant and variable, so that the absence of such a finding does not exclude the presence of allergy, but a positive finding strengthens the evidence. The red blood cell sedimentation rate is of distinct value in patients where allergy and infection are associated. We have found this test to be of value in determining the presence or absence of infection as well as the degree of infection, and it is an indispensable index in determining prognosis. More than 200 determinations of the sedimentation rate have been made and the results have been consistent with the clinical findings and diagnosis.

The occurrence of allergy and chronic sinusitis in children is not so frequent a problem as it is in the adult, and surgical measures are likewise more conservative in the child. The majority of children in our group had received only local nasal packs, irrigations, or the intranasal surgical procedures. In classifying our cases, we have included only those patients who had definite sinusitis, as evidenced by history, physical findings, and the presence of pus within the sinus cavity. In many patients, transillumination shows clouding of the antrum or other sinuses, or roentgen studies reveal clouding of the sinus areas, but no further evidence of infection can be demonstrated. Such cases have not been included in our classification of nasal allergy and chronic sinusitis.

In our series of 203 allergic children, 12 had sinusitis and nasal allergy. The average age of these patients was 12 years and the average duration of symptoms of nasal allergy was six and one-half years. Symptoms of sinusitis had been present in only two patients for the same length of time as had the symptoms of nasal allergy. Local treatment had been employed in every case, and no patient had been subjected to any radical surgical procedure. Attacks of sinusitis tended to recur over a period of years after an acute infectious disease or a severe head cold, and there was a distinct winter and spring aggravation of symptoms. Tonic measures had been used in all patients. One patient had had polyps removed. Associated clinical allergic states were present in six or 50 per cent of the patients, and was evidenced by such conditions as seasonal hay fever, asthma, eczema, and bronchitis. Three patients had conditions not associated with allergy—two had definite hypothyroidism and one had epilepsy.

A family history of allergy was noted in 10 or 83 per cent of the cases. The family history of allergy usually indicated both paternal and maternal influences.

Physical examination revealed the edematous, swollen mucous membranes typical of allergy. The findings of sinusitis were typical. Nasal polyps were present in one patient. Roentgen studies of the chest and sinuses were made in practically all cases. In one patient, roentgen studies indicated the presence of pulmonary tuberculosis, but the tuberculin test gave a negative reaction. Following the institution of an allergy regimen, roentgen studies revealed these findings to clear rapidly. Physical examination and roentgen studies suggested the presence of bronchiectasis in one patient. Two patients had signs of hypothyroidism and their basal metabolic rates were minus 21 per cent and minus 17 per cent. Laboratory studies, other than x-ray and basal metabolic rate determinations revealed secondary anemia in four patients. Eight patients, or 66 per cent, had blood eosinophilia, the average percentage being 5. The red blood cell sedimentation rate was mildly increased in a few patients.

Allergy studies were made with the three methods. In one patient, it was necessary to make the complete studies by the passive transfer method. The results of allergy studies were consistent with those obtained in the cases of bronchial asthma and perennial allergic rhinitis. An allergy regimen and tonic measures were instituted in all patients. In two patients it was necessary to use pollen desensitization and the use of thyroid, iron and iodides was employed where they were indicated in individual cases. In no instance was surgery advised.

No coöperation was obtained in 2 of 12 patients; 2, or 20 per cent, had excellent relief from their symptoms; 3 or 30 per cent,

noted good relief from symptoms; 2, or 20 per cent had fair relief, but some symptoms still persisted; in two patients the therapeutic regimen has been employed for too short a time to permit an evaluation of results and in one patient, no follow-up observation is available. Good or excellent results were obtained in 50 per cent of patients and fair relief in 20 per cent. In 30 per cent, the outcome is yet to be determined. We feel that the results obtained with allergy control are gratifying.

Gastro-Intestinal Allergy

The person who is experienced in taking histories is able to elicit mild symptoms suggestive of gastro-intestinal allergy in the majority of children who present evidences of allergy, regardless of the major problem—respiratory, cutaneous, ocular or cerebral allergy. It has already been stated that allergic manifestations are likely to be multiple, due to the diversified phenomena seen in many organs in the presence of an allergic state. Gastro-intestinal symptoms, due to disturbances in the stomach and colon, pylorospasm, cramps, colic, gaseous distention, mucous colitis, and acute and chronic diarrhea alternating with chronic constipation, may be produced by allergic factors. One likewise recognizes the symptom-complex of acute gastro-enteritis due to food allergens to which the patient is more acutely sensitive. This not infrequently occurs in children despite the fact that the parent is well acquainted with the nature of such extreme reactions. Canker sores and the more discomforting herpetic stomatitis with lesions as large as one and one-half centimeters in diameter are often due to food allergy. Investigation and control of diet in these cases has been most encouraging.

One finding has been particularly outstanding in these investigations of clinical allergy in children: invariably there is a history of inconstant, variable appetite, of food dislikes, fondness for other foods, of apathy towards eating, and then a return of appetite which is followed again by a period characterized by capriciousness. Present also, are one or more of the mild symptoms enumerated in the preceding paragraph. The major complaint may be bronchial asthma, seasonal hay fever, ocular allergy or a cutaneous lesion, but the constancy of the changeable attitude towards food persists in the majority of patients. One may immediately ascribe this finding as being due to the child's general problem and this is probably true, but it is accepted in the light that food allergy is a factor which contributes largely to the entire symptom-complex. Investigation of suspected food allergens and correction of diet based upon the results of allergy studies has given in the majority of patients, an entirely different attitude toward food, and this is characterized by constant and improved appetite and disappearance of the mild gastro-intestinal symptoms.

In this discussion of gastro-intestinal allergy, no attempt is made to analyze and present the findings in all cases in which gastro-intestinal symptoms were present. Such an analysis would necessitate a review of the majority of the 203 cases. Interest is stimulated however in a group of 20 patients who presented a very definite symptom-complex of gastro-intestinal nature. This is referred to most commonly as severe recurrent vomiting or severe cyclic vomiting.

Severe cyclic vomiting is not a disease, it is a symptom-complex dependent upon underlying systemic factors. In contrast to the clearly defined and accepted clinical picture that the patient with cyclic vomiting presents, there are diversified opinions regarding the etiological factors. On the Continent, the majority of workers describe a background of a highly sensitive, nervous child of neurotic parents, and upon this background, they consider the acute upper respiratory infections as precipitating factors. In our series of 20 patients, no history of symptoms suggesting the influence of acute respiratory infections could be obtained. It is true that a close analysis reveals a hypersensitive individual in some instances, but no more than is commonly seen in allergy of any type. American workers have approached the problem in a more analytical manner. Excessive fat, and carbohydrate diets, absorption of faulty metabolic products and hypoglycemia have been accorded consideration in the etiology of these attacks. Few workers here considered and pursued allergy as a factor in these cases. A close survey of the work presented by investigators on the Continent prove their investigation and trial of food allergy to be inadequate.

Analysis of symptoms in a child with severe cyclic vomiting suggests more than a casual relationship between this symptom-complex in childhood and the occurrence of migraine in the adult. In our series, hemicrania was not an infrequent symptom. It was particularly true of the older children that gastro-intestinal symptoms became less severe and cerebral symptoms more marked in direct relationship to age. In a recent review of patients with migraine, a percentage were noted to give a history of recurrent attacks of vomiting in early childhood. A more carefully elicited history would probably result in a higher percentage of patients experiencing such a symptom-complex in childhood.

No effort is made to explain the mechanism by which protein substances reach the tissues. That there exists some undemonstrable biliary dysfunction permitting passage of unsplit protein substances into the blood is without doubt. It is likewise conceivable that there exists an increased permeability of the intestinal mucosa, and with any de-

gree of intestinal stasis or reverse peristalsis, an overload of non-split protein substances or faulty metabolic products is thrown into the circulation, reaching the tissues as toxins and producing a violent reaction. That cyclic vomiting is a result of severe toxemia is beyond pale of doubt. The prodromal period marked by anorexia, restlessness, irritability, languor, the early appearance of fever, the active state characterized by epigastric discomfort, gaseous distention, cramps, colic, often diarrhea, nausea and extreme emesis, lasting twenty-four to forty-eight hours, and the final stage, with severe exhaustion and profound prostration followed by a slow and gradual return to a normal state within a period of several days, strengthens the contention that such a clinical picture could only result from a severe toxemia. What part food allergy plays in influencing the precipitation of this chain of symptoms, or food allergens in rendering the intestinal mucosa permeable to the passage of toxic products to the tissues cannot be definitely determined at this time. Our studies lead us to believe that severe cyclic vomiting is largely influenced by food allergy and relief of symptoms can be obtained with allergic control. Further study and longer periods of observation will aid in evaluating the influence of food allergy.

Cyclic Vomiting

We wish to submit the observations and results of twenty cases of severe cyclic vomiting in children seen since January, 1934. That these comprise 10 per cent of the total number of children treated for allergic disease in these last two years, impresses one with the frequent occurrence of this condition.

The average age of our patients was seven and one-half years. In several of these patients, symptoms had been present since infancy and in others the complaints had appeared comparatively recently, the average duration of symptoms being three and three-fourths years. The positive family history of allergy which was found in 13 or 65 per cent of these patients is approximately the same as that in any allergic condition occurring in children. Fifteen or 75 per cent of the patients with cyclic vomiting exhibited clinical manifestations of allergy. These were allergic rhinitis, asthma, urticaria, allergic conjunctivitis, and eczema. The diagnosis in these cases can usually be established by a carefully elicited personal and family history, physical examination and allergy investigation.

Complete and thorough skin tests with 120 to 150 extracts were carried out in these cases. In ten or 50 per cent of the cases, the passive transfer method was employed. In these instances, testing was necessarily limited to from 60 to 80 foods or groups of foods. In cases

where limitation of testing is encountered, we have found that the group type of food extracts is valuable.

The physical findings in these patients, at the time of their visit to the Clinic, were negative in 14 instances. Of these 14 patients in whom physical examination revealed no abnormality, diagnoses of pyelitis had been made previously in two instances. During the time these two patients have been under our observation, no evidences either by laboratory procedures, roentgen examination or complete genito-urinary investigation have been revealed which would substantiate such diagnoses.

Six or 30 per cent of the total number of patients with cyclic vomiting gave evidence on physical examination of associated pathological conditions. Three of these patients had hypertrophied tonsils and adenoids, one was suffering from malnutrition, one had rickets, and one had a deviated nasal septum. In only seven of these patients, or 35 per cent, did we find it necessary to employ complete gastro-intestinal roentgen studies to exclude any possible organic lesion, and in each of these seven cases, the findings were normal.

The routine laboratory tests were employed. In nine of the 20 patients, or 45 per cent, the blood eosinophilia varied from 2 to 11 per cent.

The treatment instituted for these 20 patients was a strict allergic regimen based upon the result of the allergy tests. General hygienic measures were routinely employed. Adequate and nutritious diets with normal gastro-intestinal elimination were emphasized.

The results of the treatment of cyclic vomiting in children indicate that food allergy is a large factor in a high percentage of patients. Thirteen patients or 76 per cent secured excellent results, four or 24 per cent showed improvement, and in three instances the patients did not coöperate with us. Therefore, all the patients who have followed the allergy regimen have noted excellent or good results.

We feel greatly encouraged with the results in this small series of patients with recurring attacks of vomiting and wish to further our observations over a greater length of time and in a larger series of cases in order to evaluate more fully the significance of food allergy in the etiology of cyclic vomiting.

CUTANEOUS ALLERGY

Allergic Eczema

It is commonly recognized that skin lesions of supposedly allergic origin are more resistant to treatment than any other allergic state.

This feature of allergic eczema in children may be due in part to the difficulty of obtaining adequate balance in a child's diet even under normal conditions. The age of the patient, the familiar background and the environmental factors are all obstacles to the successful treatment of allergic skin diseases. It is generally conceded that a higher percentage of satisfactory clinical relief is obtained in the group where personal and familial allergic states are manifested.

In our series, we have reviewed 21 cases of allergic eczema in children. The condition was present in varying degrees of severity —in some patients the lesions were present only in the antecubital fossae; in others, the lesions were limited to the face or neck, while in others, the eczematous areas were far more extensive. The average age of our patients was 7.5 years and in many of these, the personal history of eczema could be traced back to infancy. In the majority of cases, the usual onset was early in the first years of life, but in a few, the first eczematous areas were noted after the child had been capable of encountering a wider scope of environmental factors. The average duration of symptoms was five and one-tenth years.

Usually, in the allergic child, one finds a definite family history of allergic disease, and this was true in 52 per cent of our patients (11 cases). As further evidence of the association of allergic conditions, in seven of the 21 patients, 33 per cent, associated allergic states were identified. In three of the cases or 14 per cent, other skin afflictions were present—pyodermia, psoriasis and impetigo respectively as complicating factors. Hypertrophied tonsils and adenoids were present in one case.

Routine physical examinations revealed normal findings except for the eczema in 14 of the remaining 17 cases. In one, a mild degree of furunculosis was present and in two cases, urticarious lesions gave further evidence of a hypersensitive child.

Laboratory tests were made routinely and of the 21 cases, six or 34 per cent showed a blood eosinophilia of from 1 to 8 per cent (average 4 per cent). These figures are compatible with those found in eczema in the adult patient. Basal metabolic rates on two of the patients whose general condition suggested the presence of hypometabolism were recorded as minus 19 and minus 9 per cent.

Complete allergy tests were carried out by the scratch, intracutaneous and passive transfer methods. In the infants, or in those children in whom it was indicated, the passive transfer method of testing was employed. Of the 21 cases, six or 28 per cent were tested by the passive transfer method.

The parents of three children made no effort to coöperate from the

onset. A strict allergy regimen was advised and carried out in 16 of the 21 cases. In the other two, mere changing of the formulae resulted in marked improvement, both in the skin and in the general condition. The results of a strict allergy regimen were not only encouraging, but in a few cases were striking. Two of our patients secured excellent results with no return of the lesions as long as they adhered strictly and conscientiously to the dietary instructions. Nine secured improvement following allergic management and in two cases, there was no improvement. Five patients have not been followed for a sufficient period of time to warrant classification.

When those patients are included whom we have followed for a period of several months, we find that 84 per cent have secured good or excellent results, and we feel that this percentage is sufficiently high in view of the difficulties encountered in the management of this perplexing problem.

No report of our findings in ocular allergy is given here because a complete summary of this work will be published as a separate paper.

Summary

We have presented our observations made from examination of 203 allergic patients whose ages ranged from 8 months to 15 years.

Adequate investigation has been carried out in every instance. Follow-up observations over a sufficient length of time to evaluate the therapeutic regimen has been obtained in the majority of patients. A small percentage have been under control for too brief an interval to determine results, or follow-up observations have been unavailable.

Of the 203 patients, 162 or 79.8 per cent presented major symptoms of respiratory allergy, namely seasonal hay fever, seasonal hay fever and asthma, perennial allergic rhinitis, perennial allergic bronchitis, perennial bronchial asthma, chronic nasal allergy and sinusitis.

Twenty-one of the 203 patients, or 10.3 per cent, presented cutaneous lesions as the major complaint, chronic allergic eczema being most commonly noted. Atypical cutaneous lesions are not presented in this study.

Twenty or 9.9 per cent of the patients presented the symptom-complex of mild and severe cyclic vomiting. Mild symptoms of gastrointestinal allergy were present in the majority of the 203 patients. No attempt is made to analyze and classify the mild intestinal disorders.

Allergy investigation was carried out by the scratch, intracutaneous, and passive transfer methods of testing. The use of the passive transfer method was indispensable in young children where direct testing resulted in too great mental and physical shock. We employed the passive

transfer method in 57 or 28.1 per cent of the patients, using from 60 to 80 allergens in each instance. Allergic control based on the results of the passive transfer method was as accurate and satisfactory as it was following the direct methods of testing.

The results of treatment have been reviewed under each section of discussion. We feel that encouraging results have been secured in the majority of these patients, and the findings in this study emphasize the importance of complete and thorough allergy investigation in the determination of the etiology of certain respiratory, gastro-intestinal and cutaneous diseases of childhood.

Reference

1. Mullin, William V.: Surgical indications in diseases of the nasal sinuses due to allergy, Surg. Cl. North America, 15:839-849, (August) 1935.

THE ROENTGEN RAY TREATMENT OF TUBERCULOSIS OF THE MEDIASTINAL LYMPH NODES

URSUS V. PORTMANN, M.D.

Although roentgen irradiation has come to be recognized as the most satisfactory method of treating tuberculosis of the superficial lymph glands, little attention has been directed to the treatment of the same affection when it involves deeply situated glands, especially those which lie in and about the mediastinum. No doubt this is true because the latter pathological process is more obscure. However, not infrequently the pressure exerted by the inflammatory enlargement of the tracheobronchial and bronchial lymph nodes causes symptoms in many cases of tuberculosis at some stage of the disease. We have found that this difficulty may be relieved in selected cases and sometimes—particularly in children—the progress of the disease may apparently be arrested.

It seems that the rôle of the lymphatic glandular system in tuberculosis is not always fully appreciated by some clinicians, especially roentgenologists, because often the earliest signs of tuberculosis which are sought for and recognized by physical examinations or roentgenographic studies are the manifestations of the pathological processes which develop in the parenchyma of the lungs. However, it is often possible to determine with some degree of certainty, the presence of the infection in even earlier stages and possibly before pulmonary lesions have developed, if known facts about the pathogenesis and clinical course of tuberculosis are taken into consideration, and if clinicians are on the alert to intepret correctly the insidious early manifestations of tuberculosis.

It is generally recognized that tuberculosis is frequently contracted by inhalation, sometimes by ingestion, occasionally by inocculation and rarely by direct hereditary transmission of tubercle bacilli. In the vast majority of instances, tuberculosis is contracted during childhood, and the infection may become attenuated or destroyed; it may remain latent for varying periods of time or, under certain circumstances, it may become active and cause more or less severe pathological processes in various tissues of the body according to the number and virulence of the bacilli in relation to the susceptibility or resistive physiological influences of the host.

Numerous and extensive investigations have been made to determine the mode of dissemination of tubercle bacilli from their portal of entry to the tissues in which they may produce characteristic lesions. I do not intend to discuss the mode of dissemination of tubercle bacilli;

however, in some instances, the organisms may be first taken up by the lymphatic vessels at the site of entry and conveyed immediately to the adjacent lymph nodes where pathologic processes may develop, or they may be carried in the lymph channels to the thoracic duct where they are emptied into the blood stream, pass through the pulmonary and general circulation and eventually are deposited in the end vessels of any tissue of the body. It has been demonstrated by autopsy material that no matter how tubercle bacilli enter the body, the lymph glands in the immediate neighborhood of the portal of entry or contiguous groups of nodes are promptly and primarily affected, although the subjective and objective manifestations of tuberculosis may not appear until some time after the invasion of the organisms, if they appear at all. Also, it is well established by postmortem examinations that few individuals escape infection by the tubercle bacillus and that no matter when or how the organism enters the body, it is the lymph glands in and about the mediastinum that are predominately affected, the intra-abdominal nodes in a large percentage of instances and the superficial groups much less frequently, and but rarely is the disease limited to only one group of glands.

Since tuberculosis is primarily a disease of childhood and of the lymphatic glandular system, and since the glands in and about the mediastinum are predominately affected, it may justifiably be assumed that many individuals have or have had some degree of involvement of the intrathoracic groups of lymph nodes. This is particularly true of children who may have been infected but in whom the disease may not yet have developed in the lungs or other organs. But of course, physical signs or symptoms of tuberculosis do not develop in every individual who becomes infected by tubercle bacilli, especially in the early stages while the disease is still confined to the lymphatic glandular system. However, there are others, who at an early stage of the disease, do have difficulties which may be attributed to mediastinal lymphadenopathy. It is this type of patient who, if the symptoms are correctly interpreted while the disease is still in its early stage, may be relieved of distress, the general condition may be improved and the disease arrested by roentgen therapy as an adjunct to other therapeutic procedures.

There are no pathognomonic signs or symptoms of tuberculous mediastinal lymphadenitis. The diagnosis must be made largely on the basis of the history, symptoms and roentgenographic evidences rather than by physical signs. The most frequent complaints are cough, persistent fever, malaise, poor appetite and loss or no gain in weight. The cough is irritating, nonproductive, spasmodic or even paroxysmal and most distressing at night. It recurs periodically, especially during

winter months or with frequent colds to which infected children are apparently particularly susceptible. The cough may be explained on the basis of inflammatory enlargement of the tracheobronchial and bronchial lymph glands which cause pressure and irritation on the trachea or bronchi. The fact that the cough recurs when colds are contracted is probably due to recurrence of the inflammatory swelling of the nodes because the resistance of the patient is somewhat lowered by the acute illness. The fever which is associated with the cough is seldom extremely high but ranges from only slightly above normal in the morning to about 102° F. or occasionally higher in the afternoon and evening, and it may be accompanied by night sweats. Often there is a definite family history of tuberculosis and such a record should carry considerable weight in making a diagnosis of the disease in children who present the symptoms mentioned. However, occasionally no such history can be obtained and when there is no evidence of possible contact infection, there is often positive reaction to the bovine tuberculin test; therefore, it may be assumed that these patients have contracted the disease by ingestion of bacilli, possibly from milk.

A number of children in whom we have made a diagnosis of tuberculosis of the hilum lymph glands have previously had tonsillectomy performed to relieve their cough and fever. No doubt these individuals had enlarged tonsils concurrent with the more or less generalized lymphadenopathy always associated with tuberculosis, but no relief from the symptoms resulted from the operations. In this connection, we can say that we have seldom, if ever, seen benefit derived from tonsillectomy performed because the cervical lymph nodes were enlarged due to tuberculosis. Even though the tonsils may be considered to be a portal of entry for tubercle bacilli, organisms promptly enter the cervical nodes and then the tonsils are no more a focus of infection than any one of the lymph glands, so that their removal will not halt the progress of the infection. We have observed also that cervical lymphadenitis is only rarely associated with involvement of nodes about the mediastinum. If the disease involves the glands in both these locations simultaneously, it indicates an extensive and generalized involvement of the lymphatic glandular system because disease in the cervical lymph nodes does not extend directly to the mediastinum as is sometimes supposed. This is explained on the basis of the lymph drainage in the neck. The lymphatic drainage from the regions of the upper respiratory tract, including the tonsils, is to the different groups of cervical lymph nodes and then into a jugular trunk which empties into the subclavian vein; therefore, there are no direct lymphatic trunks from the cervical to the mediastinal lymph node groups. Of course, the intrathoracic nodes or other

tissues of the body may become involved from a focus in the cervical glands, but this must take place indirectly by way of the blood stream.

The physical examinations of the patients on whom we have made a diagnosis of tuberculous mediastinal lymphadenitis have given little information; at least, there have been no significant findings that consistently indicated the presence of enlarged mediastinal lymph nodes except in five adults with large masses of glands. Routine laboratory examinations, including repeated search of the sputum for tubercle bacilli, have likewise given little information. We have considered positive tuberculin reactions to be of diagnostic value and confirmatory evidence of the presence of tuberculosis according to the generally accepted criteria for these tests if both human and bovine tuberculin are employed. As previously suggested, some of our patients reacted to bovine but not to human tuberculin. Tuberculin tests should certainly be made in suspected cases in children; at least in those whose history gives no evidence of possible contact infection.

Although a positive diagnosis of active tuberculosis of the lymph nodes in and about the mediastinum should not be made from roentgenographic studies, we have found that the manifestations which are found are most suggestive in many cases when correlated with the clinical evidences of the disease. The stereoscopic posterior-anterior and lateral films of the lungs which should always be made, show an abnormal amount of hilar infiltration and often calcification out of proportion to the age of the patient. Occasionally enlarged tracheobronchial lymph nodes can be distinctly outlined in the hila, and in other instances there are irregular masses and calcifications of varying size about the hila from which infiltration extends well out into the lung fields. When healing takes place, calcifications increase in number and size, and tiny, pinhead-sized spots of calcified tubercles may be seen distributed in an irregular zone about the hila. The apices are clear in children and there are no evidences of parenchymal tubercles until after dissemination takes place to these regions through the pulmonary blood supply of the lung. When there is more extensive involvement, the mediastinal shadows are considerably widened from the hila upward and may simulate Hodgkin's disease or lymphatic leukemia. This is especially true in adults except that the outline of the nodes is not so irregularly nodular in appearance. As the disease becomes quiescent and healing takes place following treatment, a gradual increase of calcification occurs in the nodes, but if the disease progresses, tubercles may appear in the parenchyma of the lungs.

It has been suggested that in children with lymphadenitis in the hila, the roentgen appearance is that which is sometimes interpreted as a

condition due to allergy. Indeed, a fairly high percentage of our patients with lymphadenitis have been definitely allergic, but there is no reason why an individual may not be allergic and also have tuberculosis; in fact, we have reason to believe that in a great many cases in which the roentgenologic appearance and the symptoms have been explained on the basis of an allergic reaction in the chest, tuberculosis of the tracheobronchial groups of lymph nodes has been present.

We have treated another group of children who were originally referred for nose and throat examinations because it was thought that their symptoms might be caused by disease in the upper respiratory tract; indeed, the interpretation made by roentgenograms of their chests has sometimes been "upper respiratory tract infection." However, the examinations of their noses, sinuses and throats failed to reveal enough evidence of pathology to account for their difficulties. Eventually, these patients were found to have tuberculous tracheobronchial lymphadenitis. Certainly a diagnosis of "upper respiratory tract infection" by roentgen examination of the lungs is precarious in view of the fact that the lymphatic drainage from the upper air passages is not to the lungs or mediastinum. The hilar infiltrations which have been the basis for the roentgen interpretations of "upper respiratory tract infection" often present similar characteristics to what we think may often be tracheobronchial lymphadenitis.

The factors which should suggest the diagnosis of tuberculosis of the lymph glands lying in and about the mediastinum may be summarized as follows:

1. A complaint of chronic or persistent or periodic cough, unexplainable on the basis of acute infectious disease.

2. A persistent fever.

3. A history of contact with a tuberculous individual. In this connection it should be assumed that the lymphatic glandular system is primarily affected in any person who becomes infected with tubercle bacilli and that in such cases, the lymph nodes in and about the mediastinum are predominately affected.

4. Positive tuberculin tests for human or bovine tuberculosis.

5. Roentgenographic evidence of diseased lymph nodes in and about the mediastinum or of hilum tuberculosis.

Of course, it is possible for infections other than tuberculosis to cause lymphadenitis about the mediastinum, as for example whooping cough; however, these other infections are usually acute in onset and clinical course, so that there should be little difficulty in the differential diagnosis. Incidentally, it is not unlikely that the beneficial effects which

result from the roentgen ray treatment of whooping cough are largely due to the reduction in size of swollen tracheobronchial lymph nodes, the pressure from which is a factor in producing cough.

After a diagnosis of mediastinal tuberculous lymph adenitis has been satisfactorily established, small divided doses of roentgen therapy may be administered *if parenchymal lesions are absent.* We have followed the general plan usually employed for the treatment of tuberculosis of the superficial lymph node groups. Our idea has been to try to reduce the size of the swollen tracheobronchial glands in order to relieve the distressing cough and also slowly to create a reactionary fibrosis and eventual calcification and healing in the affected nodes. We believe that sometimes this procedure may increase the resistance or at least eliminate one focus of infection so that the patient is better able to combat the disease. Although we have tried to avoid treating patients in whom lesions should be demonstrated in the parenchyma of the lungs, apparently in an occasional case unrecognized pulmonary tubercles were present, because after the patients improved and the disease seemingly was arrested, roentgenograms showed miliary spots of calcification in the lung fields in a zone about the hila as well as calcified tracheobronchial nodes.

We have given treatments from every three to seven days, depending upon the severity of the cough and over a period of from two to six weeks. The technical factors employed for children have been 140 K. V. with four to six millimeters of aluminum (A. U. 0.25) and for adults 190 K. V. with one-half millimeter of copper (A. U. 0.16). Sternal and dorsal fields are used with the radiation directed to the mediastinum, which we calculate receives about 150 roentgens at each dose.

The following cases have been selected to illustrate the effectiveness of roentgen therapy for the treatment of tuberculosis of the lymph nodes about the mediastinum.

Case 1: A little girl, five years of age, had been a normal child until acute pyelitis occurred at the age of two years. She recovered from this illness and at the age of four, she had a persistent cough and it was noticed that she had a daily afternoon fever. Her tonsils were removed. The fever and cough persisted, and thorough examinations were made by competent physicians. Studies of her genito-urinary system were made, and the possibility of recurrence of pyelitis was eliminated and a roentgenologist reported that her chest was normal. Cutaneous human tuberculin tests were negative, but later she was found to react to the bovine type. When we saw her, the temperature ranged from 102° to 105°F.; she did not have chills, but drenching night sweats occurred. There was no history of contact with a tuberculous individual. She weighed 42 pounds and had weighed about the same a year previously. There were no significant physical or laboratory findings. Wassermann and repeated tests for

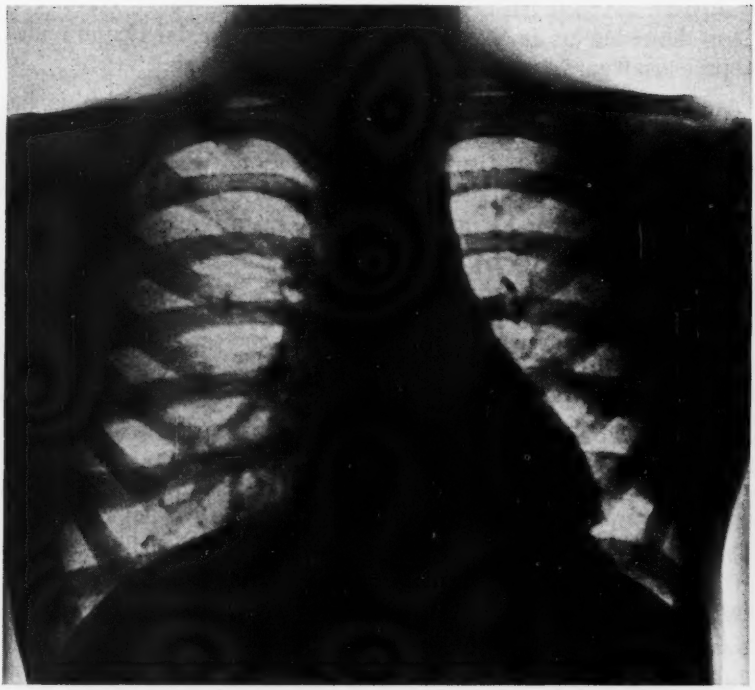

FIG. 1—CASE 1: Tuberculosis of the tracheobronchial or hilum lymph glands in a child.

undulant fever were negative, and the bovine tuberculin test was moderately positive. Roentgenographic studies of the chest (Fig. 1) revealed that the right hilum lymph nodes were definitely enlarged and an unusual amount of calcification was present. Finally, a diagnosis of hilum tuberculosis was made and the child was given bed rest, cod-liver oil and a high vitamin diet for a month, but the cough and fever persisted. Roentgen therapy was administered in small doses every second day for four times and a second course was given two weeks later. Her fever became less after the second treatment and disappeared in thirteen days; it never was higher than 100° per rectum during the next two months and she gained weight rapidly. The cough also had been eliminated and did not return during our course of observation which, unfortunately, lasted only eight months.

Case 2: This boy was first seen at the age of four years, when he was referred to the Clinic for tonsillectomy. The history revealed that he had had frequent sore throats, a poor appetite, that he fatigued easily and that he had not gained in weight since an attack of whooping cough six months previously. His mother had once had pulmonary tuberculosis and his father suffered from tuberculous iritis. Roentgenograms made prior to operation gave positive evidence of fibrous and calcific infiltration in the right hilum with apparent enlargement of the lymph nodes, so that a roentgen diagnosis of purile tuberculosis was

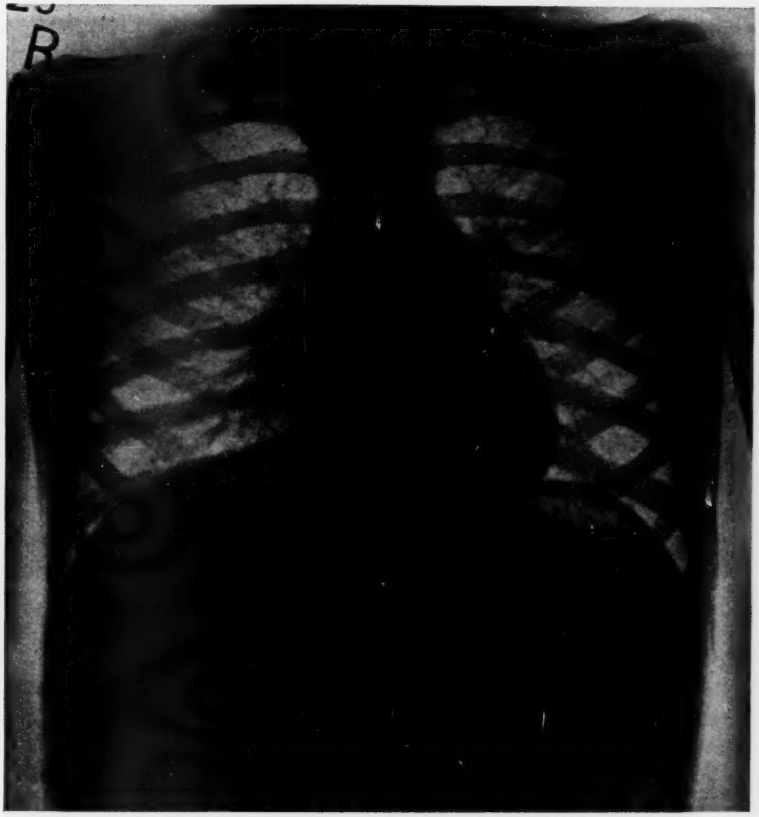

FIG. 2—CASE 2: Tuberculosis of the tracheobronchial or hilum lymph glands. Condition considered to be due to upper respiratory tract infection from tonsils.

made. But the physical and other examinations revealed no evidence of active disease, though he reacted positively to human tuberculin. Tonsillectomy was performed and following this, the temperature remained normal during three days' observation. However, rest in bed and general protective measures were advised and religiously carried out. When the patient was seen one year later, he had made no progress. He had not gained in weight, he was easily fatigued, he often had a temperature of 101.5°F., and sometimes he had night sweats and a cough. On examination, there were no significant physical findings except that the cervical lymph glands were palpably enlarged. Roentgenographic studies (Fig. 2) showed the same condition that had been described previously. At this time, there was satisfactory evidence of active tuberculosis of the tracheobronchial glands and, following the first treatment, a sharp febrile reaction (104°F.) took place, but the temperature promptly subsided in twenty-four hours, and during the next week was lower than at any time during the previous two weeks. The cough and night sweats disappeared entirely after the second

FIG. 3—CASE 2: Calcification of tuberculous tracheobronchial lymph nodes in the same patient after roentgen ray treatment. The condition is arrested or healed six years later.

treatment and his gain in weight was twelve pounds in six months. During the next year, he had one or two attacks of coughing associated with colds, and his parents promptly brought him in for treatment which was followed by relief. For three years, this patient has been without evidence of active disease and roentgenograms of his chest (Fig. 3) taken recently show calcified lymph nodes about the hilum of each lung.

Case 3: A girl of seven years was brought in because she had had periodic, severe attacks of paroxysmal, unproductive cough for the past four years. She had never had any other illness. Her grandfather is a physician, and therefore she had had numerous, complete medical examinations. There was no definite history of tuberculosis in the family. Her coughing attacks always came during the winter months, beginning in November. Each attack would last for several hours, usually coming on at night and persisting for four or five days, and they recurred about every three or four weeks. The temperature had never been

FIG. 4—CASE 3: Tuberculous tracheobronchial lymphadenitis that had been considered a condition due to allergy.

very high, but some fever always accompanied the attacks. Numerous tests had been made in an effort to explain her condition on an allergic basis, but without avail. She was referred to us because it was thought that she had sinus infections but this was not corroborated by our examination. The child was definitely undernourished, but complete physical and laboratory examinations gave no explanation for the condition. Bovine tuberculin tests were moderately positive. Roentgenographic studies of her chest (Fig. 4) showed some enlargement of the tracheobronchial groups of lymph nodes, and on this basis a diagnosis of tracheobronchial lymphadenitis was entertained. Roentgen therapy was administered at the beginning of her next cycle of coughing, and this attack was promptly aborted. Treatments were continued each week for three times and the winter passed without another attack of coughing or fever. The following winter, the child caught cold and began to cough, but a treatment the next day relieved her and the parents felt that another attack had been prevented. During the past three years, she has been entirely free from fever or cough and is developing satisfactorily without evidence of tuberculosis.

Case 4: A woman, 25 years of age, was first seen in 1930 and gave the history that her mother, father and sister had died from pulmonary tuberculosis. She had always had indifferent health and was known to be extremely allergic to several proteins. In 1928, a persistent fever developed, but many examinations by competent physicians gave no definite explanation for it, though tuberculosis was suspected. She gradually improved, but about one year later, she contracted a cold which was followed by a persistent nonproductive cough and fever. More examinations were made, and she was told that she did not have

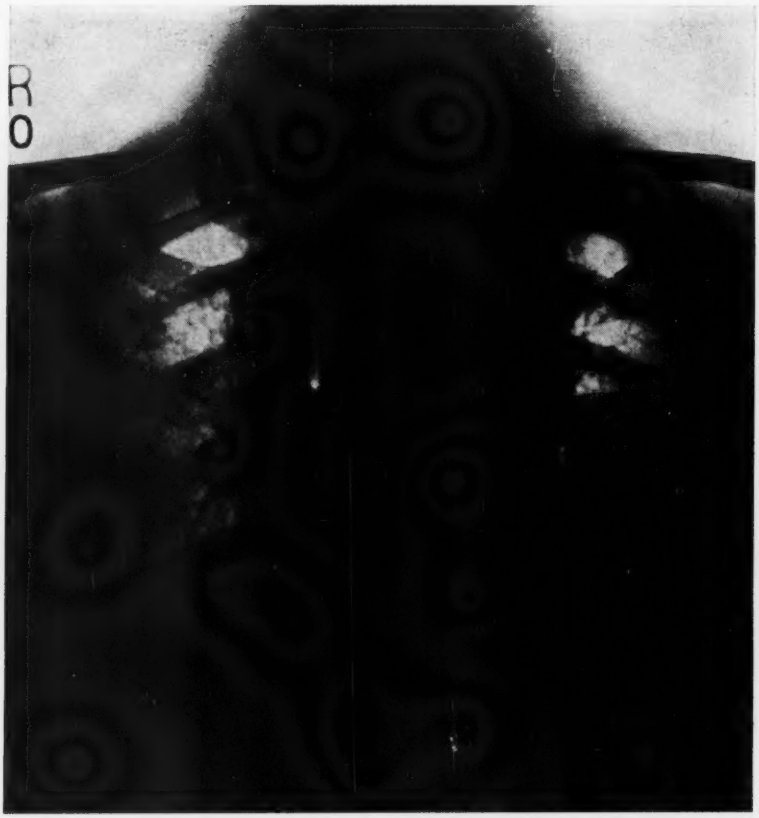

FIG. 5—CASE 4: Tuberculosis of the mediastinal lymph nodes in an adult. Simulates Hodgkin's disease or lymphatic leukemia. Before roentgen therapy in 1930.

tuberculosis. After she recovered from this attack of illness, she was married and soon became pregnant. The fever and cough returned, and tubercle bacilli were said to have been found in her sputum. A therapeutic abortion was performed and she entered a sanitarium. While there, she had several attacks of profuse menorrhagia but the condition gradually improved, the cough disappeared and she gained eleven pounds in weight. At this time, the cervical lymph nodes began to enlarge. Although her general health remained good for some weeks, she occasionally had fever and cough, and the cervical glands were often painful and they gradually enlarged. A roentgenogram of the chest which was made at this time showed a mediastinal mass and the possibility of Hodgkin's disease was suggested. A course of deep x-ray therapy was begun but after the first dose she became sick, she was nauseated, her fever rose and she was dyspneic, so the treatment was discontinued. We first saw her a few weeks later. There was no clinical evidence of parenchymal tuberculosis, but physical signs of a mediastinal mass were present. There were very large,

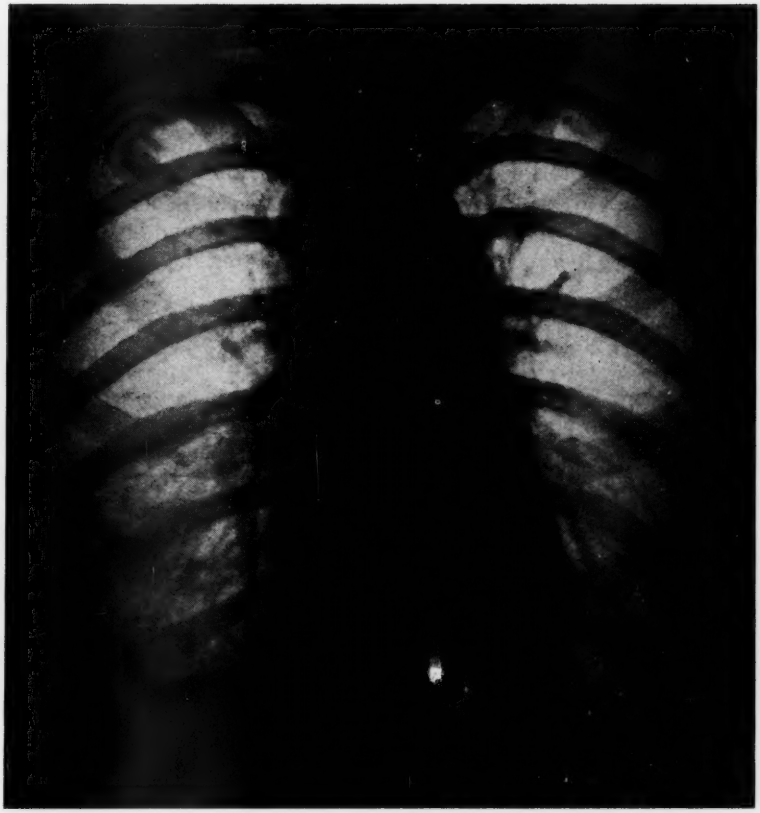

FIG. 6—CASE 4: Same patient four years after roentgen therapy and now without evidence of the disease.

nodular, coalescent masses of glands in both sides of the neck. Several examinations of the sputum showed no tubercle bacilli. Roentgenographic studies (Fig. 5) showed a large confluent mass in the mediastinum and about the roots of both lungs without evidence of parenchymal pulmonary disease. The temperature was about 102°F. at all times and a cough was present. A cervical node was excised and proved by microscopic examination to be tuberculous. Roentgen therapy was administered to the cervical and mediastinal areas in very small doses over a period of three weeks. The enlarged nodes were reduced in size, though drainage continued from the biopsy wound. The temperature returned to normal and the cough disappeared. She was returned home and continued roentgen therapy under Dr. J. F. McCullough of Pittsburgh. Within a few months, the drainage from her wound had ceased and the lymphadenopathy had practically disappeared as did any other evidence of tuberculosis, and she gained twenty pounds in weight. Although she has been very well for five years and recent roentgenograms of her chest (Fig. 6) show no evidence of

disease, we do not believe she is completely cured, although she derived unquestionable benefit from her treatment.

Conclusions

Tuberculosis of the lymph nodes about the mediastinum should be suspected, especially in children who have persistent fever and cough. If the diagnosis of this condition can be made before parenchymal lung lesions develop, the disease is probably in a comparatively early stage and roentgen therapy will often relieve the symptoms and be a valuable adjunct to other therapeutic procedures in arresting the disease.

THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

The Frank E. Bunts Educational Institute announces the second graduate review course in "Cardiovascular and Blood Diseases" on March 16, 17, 18, 1936.

A complete outline of the course and application blank will be found on succeeding pages of this Quarterly.

CARDIOVASCULAR AND BLOOD DISEASES

Monday, March 16, 1936

8:00– 8:45 A. M.	Registration	
8:45– 9:00 A. M.	Introductory Remarks	Dr. George Crile
9:00– 9:50 A. M.	Rheumatic Heart Disease	Dr. A. C. Ernstene
10:00–10:25 A. M.	Luetic Aortitis	Dr. A. C. Ernstene
10:25–10:50 A. M.	Treatment of Luetic Aortitis	Dr. E. W. Netherton
11:00–11:50 A. M.	Essential Hypertension and Hypertensive Heart Disease	Dr. R. H. McDonald
12:00 Noon–12:30 P. M.	Ophthalmoscopic Findings in Hypertension	Dr. A. D. Ruedemann
12:30– 1:30 P. M.	Luncheon	
1:30– 2:20 P. M.	Technic of a Blood Examination	Dr. R. L. Haden
2:30– 3:20 P. M.	Classification of the Anemias and Leukemias	Dr. R. L. Haden
3:30– 4:20 P. M.	Pernicious Anemia	Dr. William B. Castle
4:30– 5:20 P. M.	Relation of Lymphadenopathy and Splenic Disease to Diseases of the Blood	Dr. Bruce K. Wiseman
8:15 P. M.	Frank E. Bunts Lecture: Dietary Deficiency Diseases	Dr. William B. Castle

Tuesday, March 17, 1936

9:00– 9:50 A. M.	Cardiac Arrhythmias: Types and Their Clinical Recognition	Dr. A. C. Ernstene
10:00–10:50 A. M.	Neurocirculatory Asthenia	Dr. E. P. McCullagh
11:00–11:25 A. M.	Congenital Heart Disease	Dr. A. C. Ernstene
11:30–11:50 A. M.	Cardiac Asthma	Dr. A. C. Ernstene
12:00 Noon–12:30 P. M.	Surgical Lesions of the Cerebral Vessels	Dr. W. J. Gardner

SURGICAL CLINICS

8:30– 9:20 A. M.	The Treatment of Varicose Veins	Dr. T. E. Jones
9:30–11:20 A. M.	The Surgical Treatment of Essential Hypertension	Dr. George Crile
11:30 A. M.–12:00 Noon	Demonstration of Injection of Posterior Tibial Nerve in the Study of Vascular Disease of the Lower Extremity	Dr. J. A. Dickson
12:30– 1:30 P. M.	Luncheon	

Tuesday, March 17, 1936

1:30– 2:20 P. M.	The Heart in Relation to General Anesthesia and Surgery	Dr. Fred M. Smith
2:30– 3:20 P. M.	The Bone Marrow in Relation to Diseases of the Blood	Dr. Charles A. Doan
3:30– 4:00 P. M.	Treatment of Leukemia and Hodgkin's Disease by Radiation	Dr. U. V. Portman
4:10– 4:50 P. M.	Qualitative Changes in the Leukocytes	Dr. R. L. Haden
5:00– 5:30 P. M.	Demonstration of Natural Color Photomicrographs of the Leukocytes	Dr. R. L. Haden
8:15 P. M.	Frank E. Bunts Lecture: Newer Concepts in the Treatment of Coronary Artery Disease	Dr. Fred M. Smith

Wednesday, March 18, 1936

9:00– 9:50 A. M.	The Anemias Other than Pernicious Anemia	Dr. R. L. Haden
10:00–10:50 A. M.	Agranulocytosis	Dr. R. L. Haden
11:00–11:30 A. M.	Diseases of the Blood in Relation to Surgery	Dr. George Crile, Jr.
11:40 A. M.–12:30 P. M.	Hemorrhagic Diseases	Dr. R. L. Haden
12:30– 1:30 P. M.	Luncheon	
1:30– 2:20 P. M.	The Roentgen Aspects of Heart Disease	Dr. David Steel
2:30– 2:55 P. M.	The Heart in Hyperthyroidism and Hypothyroidism	Dr. A. C. Ernstene
3:00– 3:50 P. M.	Peripheral Vascular Disease	Dr. John Tucker
4:00– 4:50 P. M.	The Use of Drugs in the Treatment of Heart Disease	Dr. A. C. Ernstene

Demonstrations

The following demonstrations will be presented daily from 1:00 to 1:30:

1. Methods of Examination of the Blood.
2. The Technic of Venous Pressure Measurements and Their Clinical Importance.
3. The Measurement of Skin Temperature.
4. Visualization of the Capillaries of the Nail Bed.
5. Visualization of Conjunctival Capillaries.
6. Methods of Blood Transfusion.

REGISTRATION BLANK

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I am enclosing a check for $5.00 and the remainder of the fee, $5.00, will be paid on registration, March 16th.

Name.....

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Medical School from which Graduated.

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